



Model Driven Paediatric European Digital Repository

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Introduction

The purpose of this document is to provide an overview of the various dissemination materials produced within the last reporting period and made available online on the project website.

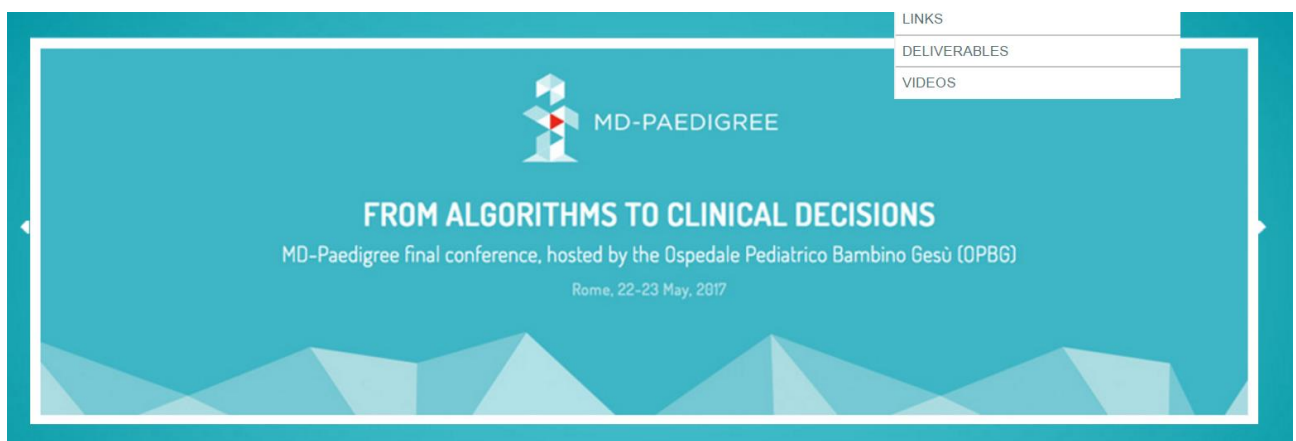
These materials have been produced in view of maximising the project outreach when attending relevant Dissemination events (e.g. MD-Paedigree Final Conference, or other public events) and in the context of the website and social media activity.

Particular attention was given to the Final Conference (Rome, 22-23 May 2017), for which a series of dedicated materials have been produced (for more details, see D18.7, "MD-Paedigree Final Conference").

Website(s)

During the last period, **banners** referred to old events have been substituted in the Home Page of the project website with new ones:

- The **MD-Paedigree Final Conference banner**, linking to a dedicated platform (see below);



- The **newsletter latest issue banner**, linking to the corresponding page (home > dashboard > newsletter > MD-Paedigree Newsletter | Double Issue 6-7).



The homepage was also updated with a **You Tube plugin window**, where the Live Stream of the conference on the main room was made available in real time through the Ospedale Pediatrico Bambino Gesù account.



The website also included an **Eventbrite plugin**, linked to the Eventbrite page of the event, which has been available until the week before the event, when registration procedures were closed.

 A screenshot of an Eventbrite event page. The event title is 'FROM ALGORITHMS TO CLINICAL DECISIONS' by MD-PAEDIGREE, held in Rome on May 22-23, 2017. The page shows the event details, including the date and time (Mon, 22 May 2017, 09:00 – Tue, 23 May 2017, 14:30 CEST), the location (Viale Ferdinando Baldelli, 38, Rome), and a description of the event. The event is marked as 'Sales Ended' and is free of charge. A 'DETAILS' button is visible.

DESCRIPTION

The event, which will be held at the Auditorium San Paolo, will gather experts from all around the world, discussing key issues regarding the application of state-of-the-art technologies to the paediatric care. The role of Clinical Decision Support Systems will be explored, with specific attention to their validation and final translation in the routine clinical practice.

DATE AND TIME

Mon, 22 May 2017, 09:00 – Tue, 23 May 2017, 14:30 CEST
[Add to Calendar](#)

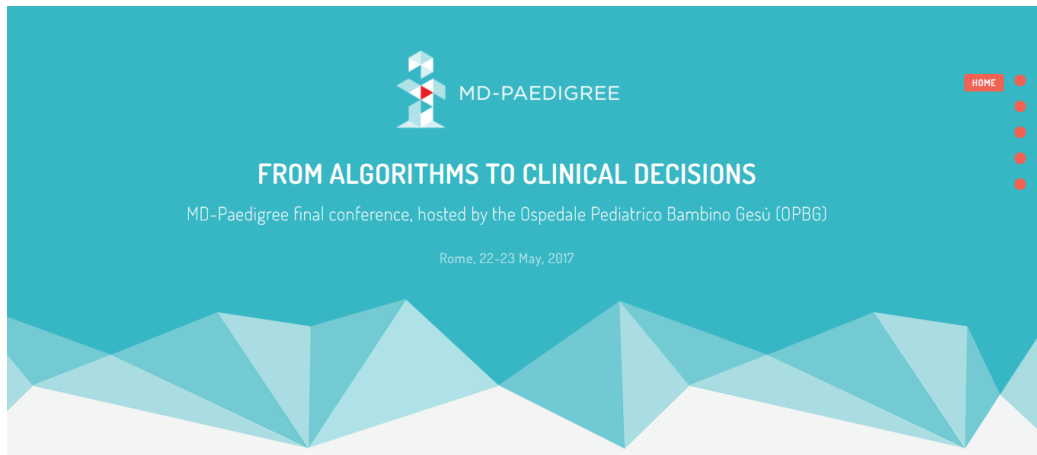
LOCATION

Rome
 Viale Ferdinando Baldelli, 38
 Rome
[View Map](#)

The MD-Paedigree Final Conference webpage

As mentioned above, a dedicated conference web page has been created within the same website domain (<http://www.md-paedigree.eu/conference/>) in order to allow a one-page layout direct access for all events details, including:

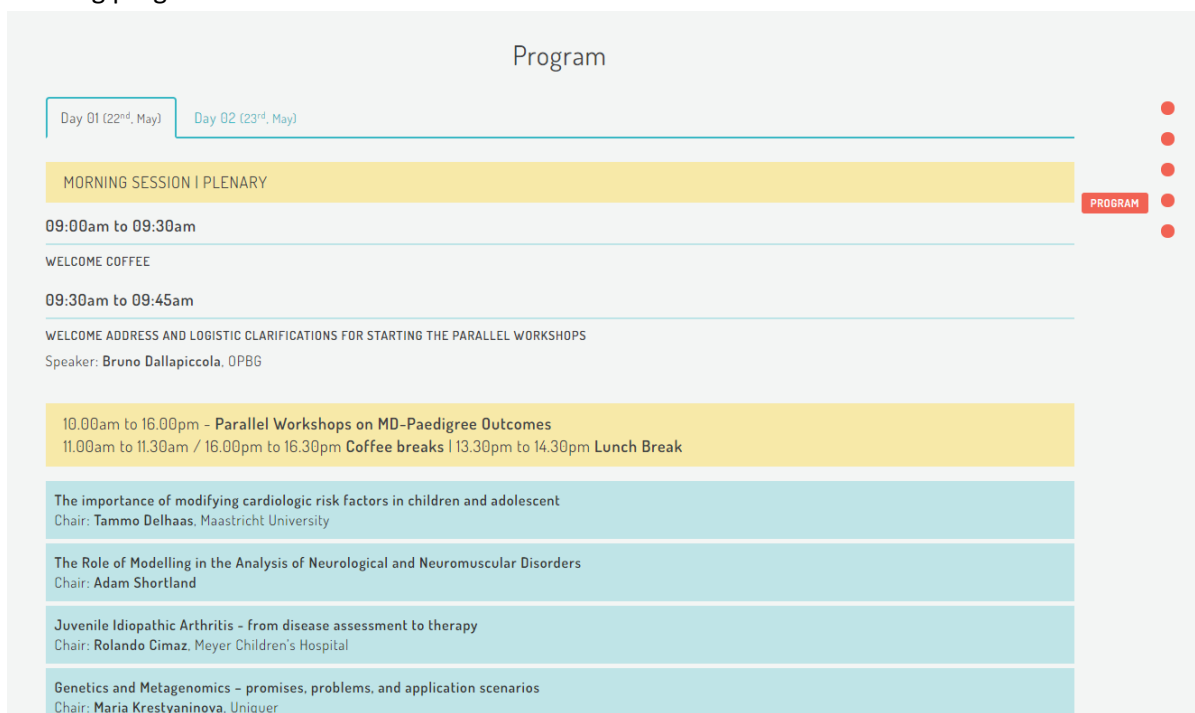
- title, date and place;



- most important themes;



- meeting program




Posters and brochures


Printed dissemination materials have been prepared in view of the Final Conference and made available on the project website, including:

- a **brochure** of the event, to be distributed at public events and conferences, providing a general overview of its contents and program;


THE MEETING AT A GLANCE



CDSSs – What's new?
State-of-the-art CDSSs presented for the first time by the MD-Paedigree developers from different European research institutions





Meet experts
World-renowned clinicians all in the same place, discussing best applications and use case scenarios of CDSSs in the clinical setting





Validation challenge
How to bring innovation in clinical practice? Let's discuss models validation and applicability in the clinical routine


CONSORTIUM




























































This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 600932

www.md-paedigree.eu/conference



FROM ALGORITHMS TO CLINICAL DECISIONS

MD-Paedigree Final Conference,
Rome, 22-23 May, 2017

Ospedale Pediatrico Bambino Gesù
Auditorium S. Paolo
Viale Ferdinando Baldelli, 38

CONTENTS

The MD-Paedigree Final Conference "FROM ALGORITHMS TO CLINICAL DECISIONS" will travel through the most innovative clinical decision support systems in paediatric cardiology, rheumatology and neurology implemented throughout the four years of the MD-P project, to be presented by their developers from all around Europe.

The meeting will be also the occasion to discuss with world-renowned physicians of the field the results of the clinical validation of the newly-developed computational models and bioinformatic tools with actual patients' data, as well as to foresee their potential application and possible use case scenarios in the clinical setting, to have an insight of the eHealth-based personalised medicine of the forthcoming future.

PROGRAMME

Day one (22nd May)
Day two (23rd May)

PARALLEL WORKSHOPS ON MD-PAEDIGREE OUTCOMES

The importance of modifying cardiologic risk factors in children and adolescent
Tammo Delhaas, Maastricht University

The role of modelling in the analysis of Neurological and Neuromuscular Disorders
Adam Shortland, Consultant Clinical Scientist, Guy's & St Thomas' NHS Foundation Trust

Juvenile Idiopathic Arthritis - from disease assessment to therapy - Rolando Cimaz, Meyer Children's Hospital

Genetics and Metagenomics - promises, problems, and application scenarios - Maria Krestyaninova, Uniquier

The role of digital e-infrastructure and data analytics tools for clinical research and everyday clinical practice
Alberto Sanna, Ospedale San Raffaele

Ethical and legal implications of MD-Paedigree's vision
Rocco Panetta, Italian Compliance Forum

PLENARY CONFERENCE SESSION
Chair: Mariella Enoc, President, Ospedale Pediatrico Bambino Gesù

Big Data from Horizon 2020 to FP9
Marco Falzetti, Agenzia per la Promozione della Ricerca

Public health genomics towards personalised medicine
Walter Ricciardi, Istituto Superiore di Sanità

Personalised medicine's impact at the European level
Carmen Laplaza Santos, DG Connect, European Commission

Big Data and data analytics in healthcare
Torsten Niederdrank, Siemens Healthcare GmbH
Patrick Ruch, HES-SO

PLENARY CONFERENCE SESSION
Chair: Bruno Dallapiccola, Scientific Director, Ospedale Pediatrico Bambino Gesù

The clinical potential of Meta Omics
Ted Dinan, APC Microbiome Institute, Bruno Dallapiccola

What can be the role of CDSSs in paediatric clinical practice
Anthony C. Chang, iSPi, Edwin Morley-Fletcher, Lynkeus

How to win the validation challenge
Marcello Chinali, Ospedale Pediatrico Bambino Gesù; Marco Viceconti, INSIGNED; Liesbeth Geris, Director, VPH Institute; Marta Bertolaso, Biomedic Campus; Thomas Geijtenbeek, TU Delft

How to guarantee the ongoing availability of research data. From local availability to distributed access
John Ioannidis, Stanford University; David Manset, Gribila

The ethical and legal framework for within which can operate a model-driven health data repository
Laura Palazzani, Libera Università Maria Santissima Assunta


The value of a common, transnational and digitally trustable infrastructure
Benoit Schoeffler, Alimerys; Yannis Ioannidis, Athena RIC

INTERNAL REVIEW SESSION
Chair: Bruno Dallapiccola

Plenary summary of MD-Paedigree outcomes and internal reviewers' assessments
Alex Jones, Gabriele Rinelli, Tammo Delhaas, Alberto Martini, Rolando Cimaz, Jaap Harlaar, Adam Shorshand, Lorenza Putignano, Maria Krestyaninova, David Manset, Alberto Sanna, Marcello Chinali, Marta Bertolaso

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- Based on the already available posters prepared for previous events, a series of **posters** were prepared for the relevant poster area just outside the plenary room, one for each disease area;




OBESITY-RELATED CARDIOVASCULAR DISEASE RISK





ADVANCED OBESITY PHENOTYPING:
Background risk factor profiles
State-of-the-art cardiovascular measures
Detailed MRI adiposity assessment
Dynamic multi-system obesogenic food response

BIG DATA MODELLING:
Complex phenotyping reveals obesity sub-types
Custom management for each sub-type
Personalised risk assessment




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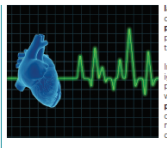
CARDIOVASCULAR DISEASE RISK IN OBESE CHILDREN

Obesity is commonly acknowledged as a **major risk factor for cardiovascular disease (CVD)**. However, the mechanism leading to the development of cardiovascular risk in obesity from childhood to adolescence to adulthood is still largely unexplored.

MD-Paedigree's study focuses on obtaining a better understanding of the early disease processes in obese children in order to tackle them in childhood, by integrating all the known biomarkers for CVD risk assessment into one common framework.

To achieve this goal, MD-Paedigree leverages on the **Big Data analytics solution** being developed within the project, such as the **'Case Reviewer'**, implemented since the FHS Health-4-Child, that enables the clinicians to **easily browse and query** patient records in a **visually meaningful way** through huge datasets of patients across Europe. This tool helps the clinicians to visualise existing clinical data from the **patient history and inter-patient similarity**, to explore large **patient cohorts**, to understand correlations between clinical factors, to **stratify patients** and to build predictive models themselves.

In addition, MD-Paedigree is building computational models with **high predictive power** to better understand the mechanism of CVD development in the future.



All these features, brought together, will allow for **individualised therapy selection, better informed diagnosis and more accurate predictions** of the patient's clinical outcomes in the future.

CLINICAL CASE SCENARIO FOR OBESITY-RELATED CARDIOVASCULAR DISEASE

Rose is a 17-year-old adolescent suffering from an Obesity-related Cardiovascular Disease. Her waist girth is 102 cm. She underwent the fasting measurement of systemic inflammation markers, the MRI evaluation of systemic inflammation of cardiac morphology and haemodynamics by echocardiography, and a cardiopulmonary exercise test. Her waist girth has significantly increased over the last 18 months demonstrating central fat distribution. Her fasting glucose is elevated and her oral glucose tolerance is impaired. Rose is dyslipidemic, with increased levels of inflammation markers.


Echocardiography demonstrates left ventricular hypertrophy with normal systolic function and impaired cardiac relaxation. The CMR evaluation and the applanation tonometry show a significant amount of pericardial fat paired with the mild diffuse fibrosis of the cardiac muscle and a reduced arterial compliance with increased wall stress and impaired endothelial function. The cardiopulmonary test reduced tolerance to physical activity, with increased oxygen consumption and an evident pathological blood pressure profile.

MD-Paedigree provides integrated information on cardiovascular structure and function, the quantitative assessment of fat distribution in the body, and metabolic and genetic data from laboratory tests. The electromechanical heart model allows understanding the mechanism of cardiac muscle and vascular dysfunction by integrating related information on systemic fibrosis, inflammation and cardiovascular mechanics. It also allows predicting the impact of selected therapies and weight loss for the specific cardiovascular function, fat distribution and exercise tolerance.

Rose's treatment is personalised and tailored using integrated information on anthropometrics, demographic data, cardiac geometry and function, vascular compliance, genetic and metabolic profiles. MD-Paedigree's accurate estimation of cardiovascular risk, prognosis of disease development and a successful therapy prediction (on previously observed cases clinical history in the digital repository) helps selecting the most effective treatment at the first disease evidence.

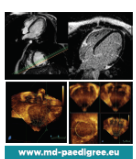
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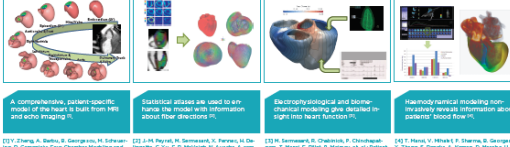






COMPUTATIONAL MODELS TO PREDICT DISEASE PROGRESSION FOR DILATED CARDIOMYOPATHIES

The clinical study is a 16 month observational longitudinal cohort study performed in three centers (Ospedale Pediatrico Bambino Gesù, Rome Italy, University College London, UK, Deutsches Herzzentrum Berlin, Germany). Enrolment of a total of 180 patients with dilated cardiomyopathy. All patients will undergo clinical evaluation, laboratory testing, genetic testing and **3D Echocardiography and MRI**.




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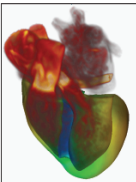
MD-PAEDIGREE AND CARDIOMYOPATHIES

More than 1 million babies are born worldwide with a congenital heart defect and it is the **1st cause of sudden cardiac arrest** and heart transplants in children. When treating cardiomyopathies one of the most difficult challenges for the clinician is to **predict the patient's outcome**. MD-Paedigree aims to provide clinicians with novel decision support tool equipped with highly advanced cardiac models to better understand how the heart is behaving, how the disease will evolve and how the patient will end in his follow-up.

Coupling advanced **image analysis techniques** with computational models of cardiac function, MD-Paedigree enhances the current standard of medical care by capturing the **main features** of the cardiovascular system and merging scattered information from different diagnostic tools, thus obtaining a generative model of the entire heart.

The MD-Paedigree models of cardiomyopathies include not only the **anatomy** of the patient's heart but also the **electrophysiology**, the **hemodynamics** and the **haemodynamic** (i.e. the blood-flow).

MD-Paedigree's patient-specific models will help clinicians to understand more in depth the **pathophysiology** and **history** of the cardiomyopathy disease and to select better, **personalised treatments** for their paediatric patients.



CLINICAL SCENARIO

Jonathan is a 12 years old boy with a Cardiomyopathy. At clinical evaluation he reported no dyspnoea at rest with some fatigue at mild exercise. He was free of cardiovascular treatment, heart rate was mildly increased and blood pressure was low-normal. A dilated left ventricle with left ventricular hypertrophy was seen by the echocardiography. Systolic function was low-normal and diastolic function analysis demonstrated increased left ventricular filling pressures. The CMR demonstrated a frankly dilated ventricle with mildly reduced ejection fraction and mild diffuse fibrosis of the cardiac muscle. The mitral annular plane was dilated and mitral insufficiency was caused by leaflet tethering. He was treated according to clinical guidelines. A follow-up clinical evaluation and echocardiogram were programmed after three months to evaluate the treatment effect.

MD-Paedigree allows Jonathan's physicians to exploit the information derived from different diagnostic techniques. MD-Paedigree provides the robust, multi-scale 4D anatomical, hemodynamic and electromechanical model to integrate all available clinical and diagnostic data. Integrated information on CMR cardiac geometry and volumes is merged to the echocardiography functional one and clinical examination hemodynamic data. Beyond that, electromechanical and haemodynamic models of the heart provided by MD-Paedigree help doctors to understand Jonathan's specific mechanism of muscle dysfunction by integrating information on muscle fibrosis and systolic mechanics, and predict the impact of therapy in reducing mitral regurgitation, filling pressure and thus relieve symptoms. Jonathan's treatment is personalised and tailored using his modelled cardiac morphology and function, integrating information on heart geometry, ejection fraction, and cardiac workload. His response to drugs is predicted by MD-Paedigree which helps physicians in prescribing the most effective treatment at the first evidence of cardiac disease, reducing the timeframe from disease evidence to medical treatment.

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PERSONALISED AND PREDICTIVE TREATMENT IN NEUROLOGICAL AND NEUROMUSCULAR DISEASES

THREE MAIN DISEASES

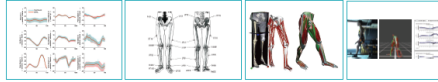
- Cerebral palsy
- Duchenne Muscular Dystrophy
- Charcot Marie Tooth disease

DATA COLLECTION

- Clinical gait analysis
- Physical examination: strength, range of motion, spasticity, selective control
- MRI and DXA imaging
- Energy expenditure
- Anamnesis and clinical context



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<p>A continuous database of clinical gait analysis and clinical context data</p>	<p>Centralised clinical partners: Quality assurance, transfer, platform & operations, protocols</p>	<p>Pathologic-specific neuromuscular modelling based on MRI and DXA scanning</p>	<p>Systematic search and prediction based on clinical and neuromuscular characteristics</p>

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NEUROLOGICAL AND NEUROMUSCULAR DISEASES

In Neurological and Neuromuscular Diseases (NND), treatments are strongly guided by maximising the walking function of the human movement system, because walking is considered an clinically meaningful by patients. MD-Paedigree focuses on three of the most common paediatric disorders within the NND disease area: Cerebral Palsy (CP), Charcot Marie Tooth disease (CMT), Duchenne Muscular Dystrophy (DMD).



MD-Paedigree has produced a standard protocol for CGA in paediatric to fully exploit the potential of CGA in supporting the clinical decision making. Furthermore, using Neuro-Musculo-Skeletal (NMS), the results of CGA are quantitatively "translated" into the function and performance of the underlying structures, i.e. muscle activation, muscle forces, and joint loads that make possible to eventually the aetiology of the pathological gait pattern of the patient under study. Essentially, the combination of gait analysis, biomechanical modelling and large scale statistical analysis will provide a powerful framework for meaningful interpretation of NND diseases.

MD-Paedigree's challenge is to fuse the scattered information on the anatomy and on the physical properties of the tissues provided by advanced imaging technologies, with the functional information provided by Clinical Gait Analysis (CGA).

A NND CLINICAL CASE SCENARIO

François is a 10 year old boy with a Neurological and Neuromuscular Disease. His medical records show a consistently significant delay in his motor development. His current level of the Gross Motor Function Classification reveals that he can walk unsupported with difficulties while walking outside. He falls over in the playground frequently, and has a very limited walking distance, due to early fatigue. Moreover, his physiotherapist is concerned that his walking pattern may deteriorate further, eventually resulting in wheelchair dependency. François is referred to a specialised paediatric centre of rehabilitation medicine, where his walking pattern is analysed in the gait laboratory. A complete re-ecording of François' gait pattern, using 3D kinematics, joint kinetics and muscle activation patterns, is performed along with metabolic measurements of the Energy Cost of Walking (ECW). From the gait analysis results, the physiotherapist concludes that hyperpronation of the calf muscles is present, while François is walking with slightly flexed knees when standing. This positioning causes compensatory hyperactivation of muscles at other levels, resulting in an overall increased ECW.

The physiotherapist should decide the therapy, but she can only rely on scattered information derived from some single cases, rather than explicit design rules. Current knowledge shows that chemo denervation of the calf muscles should normalize the hyperactivation and compensatory activation and decrease the enhanced ECW. However, it would also contribute to a higher knee flexion moment that would drive the knee in further flexion when standing, worsening his walking. The latter phenomenon would call for another therapy known to be effective to counteract knee flexion. Fortunately, the laboratory has applied the EU standards of clinical gait analysis becoming a MD-Paedigree clinical centre. MD-Paedigree disease modeling analysis shows that chemo denervation of the calf muscles could solve the problem, but the effect on knee flexion remains undecided, with an acceptable model accuracy. However, the probabilistic model supports the treatment choice and points two matched cases where chemo denervation with additional physiotherapy proved to be successful. The physiotherapist is now confident of how she will treat François.

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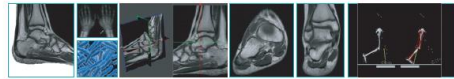
JUVENILE IDIOPATHIC ARTHRITIS: Multidimensional modelling of the disease course, Development of articulated models of the JIA affected joints, Patient-specific biomechanical simulation.

JIA is a chronic childhood disease characterized by inflammation primarily affecting the joints.

MD-Paedigree aims to implement a **Multiscale Modelling of the Joint Kinetics**, integrating body, organ and tissue levels, for automated biomarker extraction, including MRI and US data.



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<p>Integration of longitudinal clinical and multimodal data and gait cycle analysis</p>	<p>Clinical models to predict the prognosis of children and personalized biomarkers approach based on personal characteristics</p>	<p>Personalized articulated modeling of the affected joints for automated biomarker extraction, including MRI and US data</p>	<p>Personalized biomechanical model of the ankle based on MRI and gait analysis</p>

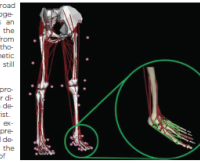
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JUVENILE IDIOPATHIC ARTHRITIS JIA

Juvenile idiopathic arthritis (JIA) - a broad term that describes a clinically heterogeneous group of arthritis which has an onset before 16 years - is currently the leading cause of childhood disability from a musculoskeletal disorder and its pathological process, including both genetic and environmental components, is still poorly understood.

Starting with the FP6 Health e-Child project, a basic framework of ICT tools for diagnosis and scoring of JIA have been designed based on image data of the wrist. MD-Paedigree further develops and extends these tools by building a comprehensive and accurate computer model derived from patient-specific data for the purpose of integrating a wider range of



joints into the model. MD-Paedigree explores the prognostic value of multidimensional data on an individual level, including modern imaging modalities, genetic and metabolomic data, as well as gait analysis data, to create patient-specific models, biomechanical models.

All the information and tools are then combined to inform the multidimensional models, with the aim of strongly impact the clinical practice on early diagnosis, prediction of disease and treatment outcomes in JIA.

CLINICAL SCENARIO

Chiara and Simona are affected by Juvenile Idiopathic Arthritis (JIA). Their age at disease onset was 4 years old and they both tested positive for antinuclear antibodies. They both had an asymmetric involvement of knee and ankle at disease onset. Within 1 year both Chiara and Simona showed arisal involvement and started a treatment with second line agents. Chiara experienced a severe and irreversible structural damage progression as revealed by a 4-year follow-up radiography. Simona developed a milder course of the disease and her 4-year follow-up radiography showed no significant signs of structural damage. Notably, at disease onset demographic, routine clinical and laboratory data did not significantly differ between these two girls. It was not possible, therefore, using traditional methods to distinguish which of them would develop a more aggressive disease. Using MD-Paedigree to set their data in a multi-scale integrated model (clinical, immunological and meta-genetic data, as well as biomechanical analysis) results, outcome predictors are identified. This means that Chiara's more severe course of the disease is determined and her need for earlier treatment is established.

A comprehensive model of JIA-related changes in two joints (knee and ankle) is available. Different imaging modalities (i.e. MRI) provide information to classify the degree of bone erosion and synovitis in both regions. For this, automated image analysis tools are developed to reduce the time necessary for performing that task and becoming independent from the individual observer. Enhanced biomechanical models are generated by adapting highly sophisticated standard models to the individual case and thus predicting locomotive changes caused by JIA. These are tested against results of a personalised gait analysis that enriches this model by providing more details about the locomotive constraints for the considered joints. The MD-Paedigree database contains morphological changes visible in the image data and clinical, immunological, genetic and metabolomic data, making access to such a large classified individual JIA cases repository helps to better predict the girls' disease progression and provide them with medication that is specifically adapted to them.

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- Beside the disease-specific posters, two new posters were created, displaying photos taken during the whole project lifetime:



Dissemination Objects (DOs) - video-interviews

A series of new videos have been produced after the project Final Conference and are available in the project website, in the relevant page.

MD-Paedigree Final Conference Video

Throughout the conference, dedicated **interviews** have been made to some of the main personalities rounded up for the occasion, including

- **Prof. Bruno Dallapiccola**, Project Coordinator;
- **Prof. Yannis Ioannidis**, President and General Director of the ATHENA Research and Innovation Center;
- **Prof. Natalia Manola**, University of Athens, Responsible of the OpenAire Project;
- **Prof. Gualtiero Ricciardi**, President of the Italian Institute of Health, namely *Istituto Superiore di Sanità*.

These interviews, together with the **video shots taken during the plenary session, parallel workshops and lunch/coffee breaks**, have been used to prepare a **video of the Final Conference**, to be presented as a final overview of the project key messages and results.

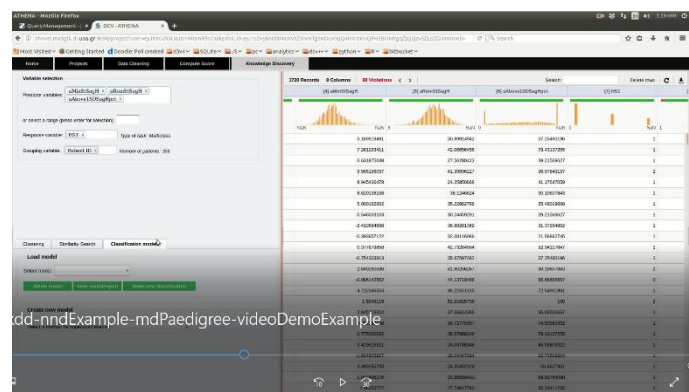


Tutorials

A series of new **videos** have been produced to illustrate the functioning of the project tools already available on MD-Paedigree platform:

- the integrated Data Curation and Validation tool for data processing tool;
- the AITON Knowledge Discovery tool;
- the Case-based Retrieval Service.

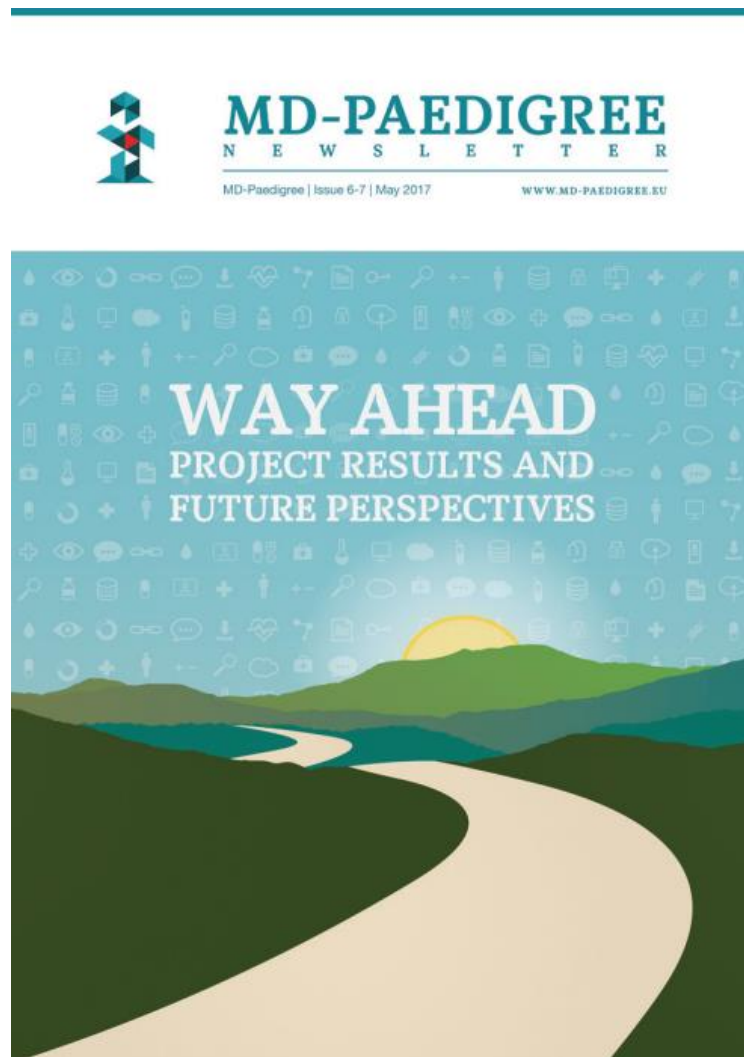
These videos have been conceived as **demos** where a typical use-case is illustrated with a hypothetical user making actions on the screen while a narrator in voiceover provides the relevant instructions and comments/explains the corresponding outputs.



Newsletter

The **final issue of the project newsletter (Issue 6-7)** has been released at the end of May and distributed during the Final Conference. As highlighted in its title, “Way ahead: project results and future perspectives”, this last issue contains the overview of the major results and tools developed throughout the project. The contents include:

- an introduction to the different project areas, research goals and clinical application scenario
- articles individually dedicated to each of the main models and big data analytics developed throughout the project, baseline principle, implementation workflow, validation in clinical setting and potential impact for clinical decision making and patient care
- an overlook of the new research initiatives fuelled by the MD-Paedigree Infostructure
- a focus dedicated to the project exploitation perspectives in the healthcare industry.



The frontpage of the Newsletter

As for the previous issues, the last one has been uploaded on the project website into the dedicated section, to be either read online through the issue plugin or downloaded in pdf format.

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