ERACoSysMed
STRATEGIC AWARENESS EVENT
"Systems Medicine in Italy – Who and Where? Present and future perspectives"

REPORT D6.4 / T6.3

ITALIAN MINISTRY OF HEALTH

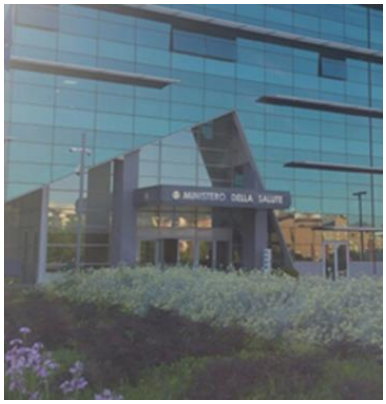
GENERAL DIRECTORATE FOR RESEARCH AND INNOVATION IN HEALTHCARE

Auditorium Biagio d'Alba

14th June 2018

ERA-NET ERACoSysMed “Systems Medicine to address clinical needs”

The ERACoSysMed “Collaboration on Systems Medicine funding to promote the implementation of systems biology approaches in clinical research and medical practice” started in January 2015 as the first ERA-Net on System Medicine under the EU Framework Programme Horizon2020. Through the Awareness events clinicians and patients are provided with information on how Systems Medicine can contribute to prevent, diagnose or treat diseases. *www.eracosysmed.eu*



Ministero della Salute

EU grant
his project has received funding from the European Union Horizon 2020 research and Innovation Programme under Grant Agreement No 643271.

Authors

Italian Ministry of Health Direzione generale della ricerca e dell’innovazione in sanità

Ufficio V Internazionalizzazione e promozione delle infrastrutture della ricerca

Dr. Giselda Scalera,

International Research Co-Operative Group MoH-IT/ISS

Dr.M.Jose Ruiz Alvarez

mj.ruizalvarez-esterno@sanita.it

Acknowledgement
It-MoH would like to thank Gina Sotgiu for the English text corrections.

Contact
It-MoH

Dr.M.Jose Ruiz Alvarez

mj.ruizalvarez-esterno@sanita.it

ERACoSysMed webpage: http://www.eracosysmed.eu Publisher

Date
June 2018

Design and layout:
IT-MoH

Content

Awareness event in Italy

Aims of the event in Italy

The awareness event, titled “Systems Medicine in Italy – Who and Where? Present and future perspectives” brought together diverse stakeholders from academia, including teaching staff, medical students, patient representatives and clinicians.

The Ministry of Health, more precisely the Directorate General for Research and Innovation in Healthcare, is committed to supporting and promoting translational research, through the IRCCS and the ISS, both nationally and internationally, and in particular to supporting and promoting the move to P4 medicine, a proactive discipline that is personalized, predictive, preventive and participatory.

Under this umbrella, increasingly accurate disease models are being produced that take into account not only genetic information, but also lifestyle, clinical history and familiarity. All this information will enable the identification of a personal risk for developing certain pathologies, the real need for a specific drug, and the adverse reaction to or benefit from one specific therapy rather than another.

Target Audience

Our Ministry is a partner of this ERA-Net on Systems Medicine under the EU Horizon2020 framework programme and it is in this context that the Workshop was organized, as part of the activities promoted by the ERACoSysMed.

This Event offered an opportunity to take stock of the implementation of a systems biology approach to clinical research and medical practice in Italy and to take a look at the future.

The working day included a first session in which international and national scientific experts contributed with an overview of current and future events regarding Systems Medicine in their Countries, including aspects concerning training, data management and related regulatory aspects.

The afternoon session focused on the research on Systems Medicine in Italy, illustrating the adopted methodological approach, the applications and their impact on clinical practice, contextualized in the field of chronic, transmissible and rare diseases. The session ended with two Italian groups, with projects financed for the Ministry in JTC-1 2015, introducing their projects and giving updates on the developments in their work.

Last but not least, the patients’ point of view on this new approach was illustrated, as were their expectations regarding the responses to complex and diversified health needs.

Reporting Rationale

This report is part of the ERACoSysMed Task 6.3 (Additional activities to create awareness of systems medicine; CSO-MOH) and refers to Deliverable D6.4.

Program

The **program** (attached) included an overview of the developing area of Systems Medicine, an interdisciplinary field of study that looks at the systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environmental interactions. During the event, research projects from different fields that apply Systems Medicine tools were presented by researchers and clinicians who study the delicate relationships between genomics, biological behavior and environmental factors.

The **second part** of the day was dedicated to brief presentations on the research carried out in the Hospital Research Centers (IRSSC) in the field of Systems Medicine, diagnosis and Personalized Medicine.

We were honored to host Dr. Cesareo, Chair of the Eracosysmed Scientific Advisory Board, and Dr. **Alberto Felice De Toni,** Rector of the University of Udine and General Secretary of the Conference of Rectors of Italian Universities, as the chairs of the First and Second Sessions for this Event. They gave an overview of Systems Medicine, including the background, its current implementations and a vision of Systems Medicine in the future, as a new approach which will integrate biological and medical data with mathematical and computational modeling in order to understand the underlying mechanisms of disease and to develop new strategies for individualized diagnosis, treatment and prevention.

Agenda

8:45-9.15	Registration
9:15-9:20	Opening and Welcome Speech - Giovanni Leonardi
SESSION I	***"The Systems Medicine: State of Art" - Chair Person Alfredo Cesario***
9:20-9:40	A Systems Medicine Overview - Gianfranco Gensini
9:40-10:00	ERACoSysMed: Systems Medicine calls and Awareness - Rob Diemel
10:00-10:20	EASYM and Training in Systems Medicine at the European level - Damjana Rozman
10:20-10:40	Data Management in Systems Medicine - Stefano Bonassi
10:40-11:00	Outcome definition and regulatory motivated research in a European Big data sharing project, HARMONY - Michael Steffens
11:00-11:30	Coffee break
11:30-11:50	The end of medicine as we know it Harald Schmidt
11:50-12:10	Italian Association of Systems Medicine Christian Pristipino
12:10-12:30	A successful example of SM approaches in the understanding of COPD Josep Roca
12:30-13:00	Open general discussion
13:00-14:00	Light lunch

SESSION II: Methodological advances and applications of research in the medical systems:

Impact on the Clinic and perspectives for patients Chair Person Alberto Felice De Toni

14:00-15:30 Research, Hospitalization and Health Care (IRCCS) Network “Clinical and Research Networking in Oncology: a substantial tool for Systems Medicine approach” IRCCS Network Alliance against Cancer (ACC)

Giovanni Apolone

“Systems medicine approach in cardiovascular disease” IRCCS Network Cardiovascular Diseases

Elena Tremoli

"Clinical and Research Networking in Neurology" IRCCS Network Neuroscience And Rehabilitation

Fabrizio Tagliavini

"A model approach to systems pediatrics" IRCCS Network Italian Developmental Age Health-IDEA

Bruno Dallapiccola

“System medicine on healthy aging and geriatrics” IRCCS Network Aging And Active Longevity (AGING)

Fabrizia Lattanzio

15:30-15:50 Rare Diseases Marco Salvatore

15:50-16:10 Clinical and Research Networking in Infectious Diseases: tool for Systems Medicine approach - Giuseppe Ippolito

16:10-16:40 ERANET ERACoSysMed - Success stories:

Systems Medicine on Transplantation Medicine: A systems medicine approach to minimize macrophage-associated interstitial fibrosis and tubular atrophy in renal allograft rejection - Massimo Locati.

Systems Medicine on Neurological Disease: Using computational tools to design personalized healthcare for Multiple Sclerosis - Antonio Uccelli Nikole Kerlero de Rosbo

16:40-17:00 From the point of view of patient associations Sabrina Nardi

17:00-17:30 Closing Remarks

Networking Cocktail

Summary of presentations

Prof Gianfranco Gensini-Department of Clinical and Experimental Medicine, Florence University-illustrated the vision of "WHAT IS IN THE NAME 'SYSTEMS MEDICINE' ? Personalized medicine, precision medicine, P4 medicine (P4= predictive, preventive, personalized and participatory) and systems medicine are different names to illustrate the common desire to establish a novel (more personalized, precise and systematic) approach in medicine. The routes via which these goals should be achieved are very similar and a core element is the integration of data from different sources, including conventional patient data, clinicopathological parameters, molecular and genetic data as well as data generated by additional new-omics technologies. New technologies that generate, store and retrieve medical and research data are driving a rapid change in clinical and translational research and ultimately in health care. Systems medicine is the interdisciplinary approach wherein physicians and clinical investigators team up with experts from the fields of biology, biostatistics, informatics, mathematics and computational modeling to develop methods to use new and stored data to the benefit of the patient. Demonstrations of improved clinical and cost effectiveness will be necessary to drive reimbursement reform and ultimately wide scale adoption. The robustness of systems oriented multimodal data when reduced and made actionable by providers and patients will further stimulate clinical utility and bring about an inflection or tipping point. This future is scheduled to arrive in daily clinical practice very soon.

Dr Rob Diemel-Senior Programme Officer at ZonMw (the Dutch Organization for Health Research and Development)-spoke on behalf of ERACoSysMed about the evolution of the ERACoSysMed calls, the funding opportunities and the awareness activities, with an overview of the consortium of Personalized Medicine and calls under the umbrella of H2020. He started by defining Systems Medicine as the implementation of systems biology approaches into medical concepts, research and practice. The application of this research model aims to understand the systems in health and disease, combining all available data (clinical, scientific) and using different models (mechanistic, dynamic, statistic). The collaboration of clinicians, biologists, modellers, bioinformaticians, geneticists, pharmacologists etc. will be the first step towards Personalized Medicine, with cost-effective health care benefitting patients, society and industry .

ERACoSysMed and CASyM aim to better understand diseases by the application of Systems Medicine and to stimulate collaboration between clinicians, systems biologists and patients. CASyM has formulated a road map for the implementation of Systems Medicine in Europe. CASyM is a network comprising hospitals, academia, industry, patients and politics. ERACoSysMed is a network of funding agencies that organizes awareness events for various stakeholder groups and that launches Systems Medicine calls aimed at consolidating interdisciplinary and transnational collaboration.

Prof Damjana Rozman-Center for Functional Genomics and Bio-Chips, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Slovenia-gave a presentation entitled "**EASyM and Training in Systems Medicine at the European level"** illustrating the European Association of Systems Medicine, a charitable association open to everyone with an interest in personalized medicine and systems medicine with a focus on the union of experimental medicine and clinical research. Integrating all relevant stakeholders, including clinicians, researchers, medical and patient organizations, industry, funders & policy makers. Future goals include intensifying collaboration with other initiatives to promote Systems Medicine training principles in Europe (ICPerMed, Elixir, Eatris, ISBE, Corbell, Fairdom….), joining efforts with EMSA, IFMSA and AMSE, regarding the need to include more mathematical principles in studies of medicine, identifying specific medical schools in Europe that would be interested in piloting a Systems Medicine course, or including this topic in a degree course, finding money to support these activities at EU level and broadening the vision concerning the importance of Systems Medicine approaches in modern, post-genome medicine.

Dr Bonasi-Unit of Clinical and Molecular Epidemiology, San Raffaele, Pisana (IRCCS)-started his presentation by illustrating the benefits of an e-HR (electronic Health Records) sharing system. The

benefits for Patients of maintaining comprehensive online records for health providers are numerous, providing necessary information more quickly and accurately as well as reducing the unnecessary duplication of tests and treatment. The main benefits for clinicians are related to more efficient and quality-assured clinical practices as well as a decrease in the amount of errors associated with paper records. Finally, Society benefits through an improvement of disease surveillance and monitoring of public health, which contributes to more comprehensive statistics for formulating public health policy, which in turn will make total health expenditure more efficient.

Data utilized for Systems Medicine is extremely valuable and contains sensitive patient information, but privacy and security concerns have yet to be specifically addressed for genomics and systems medicine. Currently, providers are relying on their existing internal privacy and security infrastructure to protect genomics data. Providers acknowledge the privacy and security risks of storing, sharing and using genomic data, but not much additional investment has been put towards this component of data management.
Genomic data needs special privacy standards and security measures to protect personal information and the integrity of research initiatives For the data Acquisition, the data should be gathered, filtered, cleaned, and moved into a ready state for analysis before the data is put in a data warehouse or any other storage solution. The acquisition of big data used to be commonly characterized by “the three Vs”: volume, velocity, and variety. While these three remain demonstrably important, providers are starting to focus on a fourth “V”: value. Providers want adaptable and time-efficient gathering, filtering, and cleaning algorithms that ensure that only the high-value forms of the data are actually processed and analyzed.
They also want to be able to structure their data in a way that can be easily translated for clinical use. Dr Bonasi ended his talk with this question : The main aim of personalized medicine is to improve patients’ lives ! but how can we measure this ??

Dr Michael Steffens-Research Division at the Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany-presented the project HARMONY: Outcome Definition and Regulatory-motivated Research in the European Big Data Sharing Project. Regulatory driven research has the potential to support drug regulation in developing and setting standards and norms for outcome evaluation in clinical trials for hematologic malignancies (HM). The presentation illustrates aims and fundamental research questions of drug regulatory science in the era of personalized and systems medicines. The importance of regulatory science was illustrated on basis of the European big data sharing project HARMONY that established a unique collaboration between academia, pharmaceutical industry, HTAs, and regulators to foster the harmonization of outcome measures and endpoint evaluation for HM. Challenges regarding different endpoints and surrogate outcome measures for overall survival were pointed out and discussed. The role of systems medicine and systems pharmacology for drug research was delineated in the light of different research strategies between academic, pharmaceutical industry and regulatory research.

Prof Harald H.H.W. Schmidt-Department of Pharmacology and Personalised Medicine, Faculty of Health, Medicine and Life Sciences, Maastricht University, the Netherlands-presented us with his vision of “**The end of medicine as we know it”.** For many years, the success rate of drug discovery and development has been in constant decline. One cause of failure is the lack of efficacy i.e. the inconsistency of observed clinical data with previous basic research and pre-clinical evidence. This dramatically poor translational success of biomedical research is most prominent for ischemic stroke, a condition with a high medical need, over a thousand experimental drug targets were unsuccessful. However, it pertains to every medical research field. Stringent statistical thresholds, reporting negative data and a systematic review / meta-analysis / pRCT approach can ensure biomedical data validity and overcome risks of bias. To facilitate the deposition and accessibility of negative data systematic reviews and meta-analysis, the pre-clinicaltrials.org database has been founded. Another reason for failure and our current imprecision in medicine are our definitions of disease, mostly by organ or symptom, not by mechanism. Systems Medicine will lead to a mechanism-based redefinition of disease and precision

diagnostics and therapies eliminating both the risk out of drug discovery but eventually also the need for further drug discovery.

Dr Pristipino illustrated the role of the Italian Association of Systems Medicine (www.assimss.it) -a network for all the professionals involved in systems science in health care. This association studies healthcare and more specifically aspects regarding quality, quantitative dimension and management. Assimss has broader field of interest such as the vision of the system medicine on the knowledge, science, management and clinics. One of its objectives is to promote the application of systems medicine through training, taxonomy, clinical trials and monitoring.

Prof Dr Josep Roca Torrent-Professor at the University of Barcelona-presented "A successful example of SM approaches in the understanding of COPD". The COPD project within the integrated care program in Barcelona was conceived as a systems medicine approach to study underlying biological mechanisms of skeletal muscle dysfunction and the phenomenon of co-morbidity clustering observed in patients suffering from chronic obstructive pulmonary disease (COPD). The overarching hypothesis was that non-pulmonary manifestations cannot solely be explained by the activity of the pulmonary disease. The presentation summarized the biomedical outcomes of the project. The results identified abnormalities in co-regulation of bioenergetics, inflammation and tissue remodelling processes, operating as central players in non-pulmonary manifestations, and a relevant role for oxidative stress as a key characteristic mechanism in these patients. The findings showed significant associations with aerobic capacity, but not with lung function. In addition, a data-driven analysis of the Medicare dataset indicated higher risk for co-morbidities in patients with COPD. Moreover, a population-health risk assessment of COPD cases in Catalonia (ES) suggested a high predictive role of co-morbidities in terms of mortality, hospitalizations, multiple hospital admissions, and high healthcare costs. These findings on mechanisms of non-pulmonary phenomena and co-morbidities, indicate the need for novel risk assessment strategies. The project outcomes strongly point out that current standards for clinical management should be complemented by a patient-oriented approach considering enhanced comorbidity prevention and management.

Giovanni Apolone spoke about Clinical and Research Networking in Oncology: a substantial tool for Systems Medicine. He explained the current scenario of Oncology in Italy, the cancer figures in Italy (about 370,000 new diagnoses/year, 1000/day; increasing incidence and decreasing mortality; average outcome: 65% survival. About 3,500,000 people living after a diagnosis of cancer, 25% cured). NHS and Research and the new trends in pipelines and clinical trials methodology. The last focus on the Italian IRCCS system and its networks. The Italian MoH, in order to increase collaboration within specific disease, has created 4 IRCCS sub-networks on specific diseases (with dedicated governance bodies and funds): Cancer (Alliance Against Cancer), Neuroscience, Cardiology and Rehabilitation. Alliance Against Cancer (AAC) is now running a study in lung cancer to develop and validate a common panel of genes (to be tested on 1000 cases) to profile patients and facilitate care and inclusion in precision medicine clinical studies. He concluded, emphasizing the necessity for strong regional, national and international collaboration and Networking that should be implemented at Institutional and not at researcher level with well-established and long standing Consortium. In his opinion, "new/novel" Consortium should be established as "Virtual Institutes" that should be multi-disciplinary (not disease oriented) and with an ad-hoc strong governance structure.

Prof. Elena Tremoli-Scientific Director of the Monzino Cardiology Centre (IRCCS) and President of the IRCCS Cardiology Network-highlighted the fact that excessive spending due to the misuse of medicines drives the need to search for cutting-edge, scientific discoveries in clinical research more quickly and efficiently. This is even more relevant for cardiovascular disease that still represents the major cause of death in the western world. Human cardiovascular diseases result from the complex interplay between perturbed molecular pathways and environmental factors rather than individual failing components. Systems-based approaches are particularly valuable in complex diseases that have multifaceted causative factors, such as cancer, diabetes mellitus, and cardiovascular diseases. Despite the adoption of life style modifications as well as evidence based therapies aimed at modifying CV

phenotypes at risk, still the issues of CV prevention and cure remain elusive. Cardiovascular pharmacogenetics can be used to identify genetic diversity markers associated with poor response or adverse reactions to drugs and there are numerous examples of genetic diversity and DNA variants as determinants of response to a drug. Moreover guideline-driven care, although effective on a population scale, fails to account for an individual unique susceptibility to disease and their response to therapeutic interventions. Systems biology can provide new avenues for understanding human diseases, identification of diagnostic disease biomarkers, development of disease treatments by revealing disease subtypes and the identification of novel therapeutic targets for diseases. The main aim of the Network is to develop synergies in the cardiovascular field among the 17 IRCCS by pooling the available know-how and triggering a multiplicative effect to achieve macroscopic objectives, such as the identification of new diagnostic strategies using prognostic and predictive factors.

Prof. Bruno Dallapiccola-*Bambino Gesù Children's Hospital, on behalf of "IRCCS Developmental Age Network "*-showed a model approach to systems paediatrics. The IRCCS Developmental Age Network (IDEA network) was established in mid-2017, by six founder Institutes, including 3 Paediatric Polyclinics, and 3 Institutes for child neuropsychiatry, intellectual disability and rehabilitation. A seventh neurological Institute has recently joined the network. Three research projects are shared, including two integrated studies for the early screening and care of neurodevelopmental disorders, and for investigating developmental brain disorders based on advanced imaging, and a clinical and genomic study of undiagnosed patients. Due to the short life of these projects, no significant findings are yet available. For this reason, Prof Dallapiccola focused on a model that came in part from the experience of the two largest Institutes of the Idea network, within the MD-Paedigree project. This was a European Commission funded, clinically led virtual physiological human project, aimed at developing a model-driven and workflow-based digital repository, leveraging an evolving information processing and knowledge discovery framework, for personalised and predictive treatments in paediatrics. The MD-Paedigree consortium included seven clinical centres, 1 multinational industry, 5 SMEs, 8 academic and research centres, from 10 EU countries, with more than 80 researchers involved, who collaborated over 4 years, until the end of 2017. The challenges addressed by this study included the development of new tools for predicting the evolution of clinical conditions, and the treatment outcomes; to support patient-specific clinical decisions by means of *in-silico* medicine modelling and analytics; and to introduce these tools in clinical practice. The study focused on four diseases, including dilated cardiomyopathy, obesity-related cardiovascular disease risk, juvenile idiopathic arthritis, and some neurological and neuromuscular diseases. A few core technological assets were implemented by the project: a clinical data repository; a set of mechanistic models of diseases, organs, and physiological functions, for simulating clinical outcomes at baseline and under different care regimens; a set of advanced analytics tools, for the identification of clinical, biomolecular and imaging predictors; several advanced search tools, to provide physicians with actionable clinical insights. A key step of the project was the validation of the predictive systems, to bridge the technology labs and clinical environments. A framework for *in silico* systems was validated, extending the traditional clinical trial practices by starting from technical verification on computational prototypes, leading to internal validation on test data sets, directing to external validation on clinical cases, at baseline and follow-up. More than 800 patients were recruited to test the predictive accuracy of analytics and simulations systems. Records from more than 50,000 additional subjects were collected from electronically documented routine care. At the end of the process, MD-Paedigree made available: an extensive clinical data repository containing information-rich records, including clinical histories, lab data, 3D-MRI studies, genetic and metagenomic profiles, and more, all available under documented access policies to academic and research centers across Europe. The system includes data curation and validation tools to foster data accuracy and normalisation; integrated advanced search and visualisation capabilities based on clinical similarity. These enable clinicians to identify and review cases relevant to the one at hand ("patients like mine") for comparative outcome analysis and more effective decision-making. The evolution from reductionism towards holism, tackled by systems medicine, still meets a number of difficulties, in particular in addressing some complex interactions in the human body, notably in the light of patients' genomics and environment. In this respect, three major drawbacks that lessen the role of genomics in systems and

personalized medicine were underlined: the unknown role of rare variants (which account for the 85% of interindividual variation) onto the phenotype; the impact of millions of postzygotic genetic modifications resulting from somatic retrotransposition; the impact of environment/life style onto human phenome.

Dr. Fabrizia Lattanzio talked about the effect of Systems Medicine on Healthy Aging and Geriatrics. The human organism could be represented as a network of networks (including genome, molecules, cells, organs, whole body and social networks) interacting with each other so that we can identify sources of damage and repair pathways, and obtain an early identification of instability of a biological network. In order to understand the process of aging and its consequence we need to decipher hallmarks of aging within the framework of interaction networks, this review highlights nine tentative hallmarks that represent common denominators of aging. These hallmarks are highly interconnected at different levels and in different scales of time and space. A major challenge is to dissect all interactions and their contribution to aging and age related diseases. In this context, aging is a phenomenon which could be well described with system biology approaches, in order to identify targets for healthy aging… Moreover, the paradigm of the research of treatments for the single chronic pathologies is constantly moving towards the search for biological pathways common to these pathologies with the aim of identifying innovative treatments. The biological pathways that underlie the aging process are probably the future of research in this sense. In conclusion, Dr Lattanzio illustrated the Report-AGE project: a permanent epidemiological observatory to identify clinical and biological markers of health outcomes in elderly hospitalized patients in Italy.

Prof. Salvatore-Researcher from the Rare Disease Center (Italian National Institute of Health)- presented the genetic aspect of E-rare diseases and how Systems Medicine approaches are used for accurate diagnosis and efficient treatment of his patients.

Rare diseases (RDs) are often life-threatening or chronically debilitating conditions with a low prevalence and a high level of complexity. In the EU, a disease is considered rare when it affects no more than 1 per 2000 persons. Though individually rare, taken together RDs are common. There are around 6000–7000 rare genetic diseases, the most rare of which are estimated to affect about 1/2,000,000 patients.

Supporting collaboration and optimizing the use of limited resources by data sharing is particularly needed, due to the low individual prevalence and the scarcity of information related to each disease. RD registries, databases, and biobanks constitute key instruments for increasing knowledge, especially when they allow the pooling of -omics, clinical, and phenotypic data (used in a standardized way i.e. through Human Phenotype Ontology, HPO).

Changing approach to RDs from a “usual” to an “un-usual” way have great potential in the identification of shared pathways among different conditions: sharing information regarding research results from common signalling pathways involved in different rare (and common) diseases could improve knowledge and shed light on a whole range of clinically different, but biochemically similar disorders.

This approach will be facilitated by the activity of 24 European Reference Networks (ERNs). ERNs are virtual networks involving healthcare providers across Europe. They aim to facilitate the approach on complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources.

Undiagnosed Rare Diseases offer an important example of application of System Medicine due to the necessity of creating an integrated and collaborative community across multiple Countries and among laboratory and clinical investigators prepared to investigate the pathophysiology of these newly recognized and rare diseases. Sharing information at global level and among different expertises can significantly facilitate research into the aetiology and the pathogenesis of undiagnosed diseases, by collecting and sharing standardized, high-quality clinical and laboratory data, including genotyping, phenotyping, and documentation of environmental exposures.

Possible results of the application of a system approach is the identification of biomarkers to monitor diagnosis and responses to therapy by accelerating research also with Next-generation sequencing instruments.

RDs can be considered as a benchmark for testing Systems Medicine models and can help us to understand other diseases, thus leading the way to personalized medicine.

Prof Giuseppe Ippolito presented his work "Clinical and Research Networking in Infectious Diseases: tool for Systems Medicine approach" that combines advanced experimental and clinical approaches to studying infectious disease with the vision of the System Medicine. Systems biology of microbial infection aims at the development of testable mathematical and computational models of host-pathogen interactions that have predictive power for diagnosis and therapy by focusing on biomarkers and drug targets. In three studies within the Human Functional Genomics Project, the effect of environmental and non-genetic host factors of the genetic make-up of the host and of the intestinal microbiome on the cytokine responses in humans were assessed. This comprehensive and highly integrated systems biology application seeks to delineate the complex host responses. In the context of infectious diseases, several issues can be addressed using this wide approach (early diagnosis, host pathogen interaction, vaccine effectiveness, drug targets identification, Infection severity susceptibility and Protection signature). Major challenges for Systems Medicine are the rise of antibiotic resistance, emerging infectious disease outbreaks, use of immuno-modulatory treatment (Antibodies, CAR-T cells) and gene-editing approach (CRISP). One thing is clear, as we embark into an era of increasing antimicrobial resistance coupled with the routine use of advanced immune modulating agents delivering deep, potent immune suppression, the role of personalized medicine to better understand the clinical outcomes of infectious complications becomes more critical. According to the paradigm of precision medicine, the administration of agents targeting the molecular alteration detected in a particular patient's tumour reduces uncertainty in the clinical management of that patient. Approaches to precision medicine can lead, paradoxically, to increased levels of uncertainty. Recommendations are offered for physicians on how to better navigate new uncertainties in precision medicine. The talk ended with a vision of the needs for networking for EIDs in the field of basic and translational research: complementarily, multidisciplinary, more funding; Public Health: coordination and standardization of policies, possibility of transnational interventions; Diagnostic issues: sharing of diagnostic protocols, samples, reagents, and personnel; Clinical and infection control issues: expert consultation, sharing of "real-life" experiences, standardization of infection control procedures.

Concluding panel

The day concluded with a presentation and open discussion with the participation of two researcher groups funded by ERACoSysMed.

Dr Uccelli and **Dr Kerlero de Rosbo** presented their project "Using computational tools to design personalized healthcare for Multiple Sclerosis". The consortium integrates different types of clinical data and develops software that will match an individual patient to a specific disease subgroup, allowing clinicians to better predict the course of the disease and make personalized therapeutic decisions. Development of personalized health care for complex diseases like Multiple Sclerosis (MS) is hindered by the poor understanding of the biological processes underlying the disease and by patient heterogeneity. These are significant shortcomings in terms of monitoring or predicting the disease course, as well as in predicting the most efficacious or safer therapies. The aim is to apply systems medicine approaches combining integrative omics, imaging and clinical data with computational tools, to develop algorithms that can be used in clinical practice to define the prognosis and select the best therapeutic approach. Through 4 European centers in Spain, Germany, Norway, and Italy, a cohort of 329 MS patients and 90 control individuals have been recruited. In addition to clinical phenotype and imaging (MRI, OCT) to quantify central nervous system damage, data on genomics is being collected to evaluate the patient's genetic predisposition, phosphoproteomics to assess the activity of signaling

pathways involved in the immune response, and cytomics to capture the dynamics of the autoimmune response.

Cytomics data obtained in four European centers by flow cytometry of immune cell subsets in PBMC samples from 246 MS patients (age 42.5 ±_10 years; sex: 67.5% female; disease duration: 10.6 ±_8 years; subtype: 80% RRMS; 20% PMS; mean EDSS: 2.4 ±_1.7) and 77 healthy controls (HC) have been presented. Assays were strictly standardized using specifically prepared antibody-cocktail lyotubes. Differences between groups were assessed by analysis of covariance adjusting for sex and age.

Significant differences in immune cell subpopulations in MS patients compared to HC for naïve and total regulatory CD4+ T cells and for regulatory B cells were found. Comparison with HC indicated that: MS patients have significantly lower percentages of naïve Treg and Th1/17 cells and higher percentages of total Treg and Breg cells; patients receiving high-efficacy drugs, in particular Fingolimod, have less naive-Treg and Th1/17 cells and more total Treg and Breg cells than patients on other treatments. Together with markers revealed through the other omics in combination with clinical and imaging data, cytomics markers will be used to search for prognostic and predictive biomarkers and develop clinical decision support systems for improving management of MS.

Massimo Locati illustrated the project " A system medicine approach to minimize macrophage-associated interstitial fibrosis and tubular atrophy in renal allograft rejection " where target macrophages having negative effects on transplanted organs, while preserving delicate immunological balance required for long-term graft survival. Expected results include dynamic (agent-based) mathematical models reflecting essential mechanisms leading to IF/TA , validation with biopsy-based large-scale clinical data, making workflows for biopsy evaluation guiding medical decisions.

Patient Organizations:

When considering disease, health, and wellness, the patient must be at the center, with common ground for discussion and models for understanding**.** Professionals and patients need to act in agreement with the data interface. From the bedside, the physicians/nurses must collect and sort patient information and then, filter, classify and share this data in order to identify specific outcomes to apply to individual patients. Systems medicine should drive research to benefit the patient.

The models and principles should organize future information and reduce the inherent complexity—be coherent, achieve clarity, and communicate cause and effect in a simplified, understandable way.

Evaluation

The presentations aimed to better define the field of Systems Medicine and its future applications in Italy.

Target audience

The total number of registers was 126 plus 22 speakers (from Italy, Germany, Slovenia, Spain, the Netherlands) including the important participation of four Italian regions (Emilia-Romagna, Lazio, Lombardy and Liguria). Finally, around 110 people attended the meeting. Among these were Physicians / clinicians working in hospitals and medical research centers (24%) and systems biologists (27%). In addition to these also stakeholders from the industry, regulatory agencies, patient representatives, funding and policy agencies attended the meeting.

Fig 1A and 1B: Geographic distribution Target audience

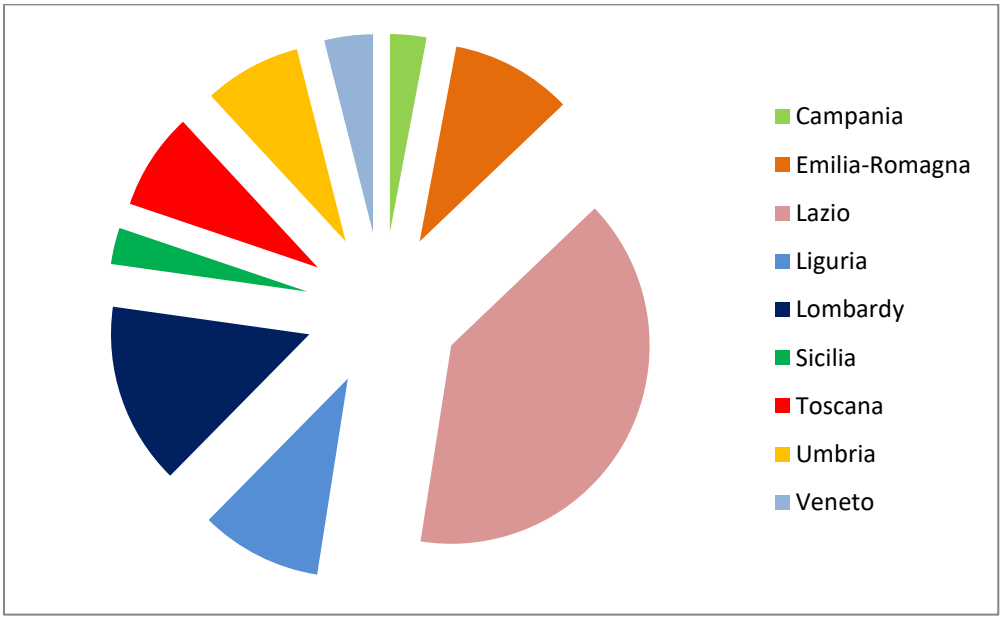


Fig. 2. Expertise distribution Target audience

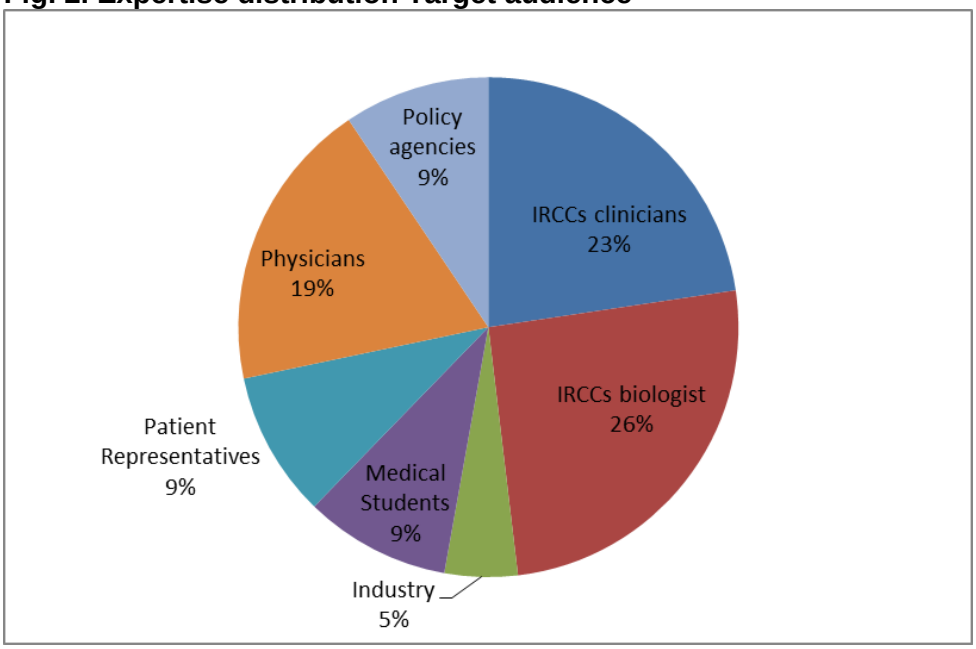
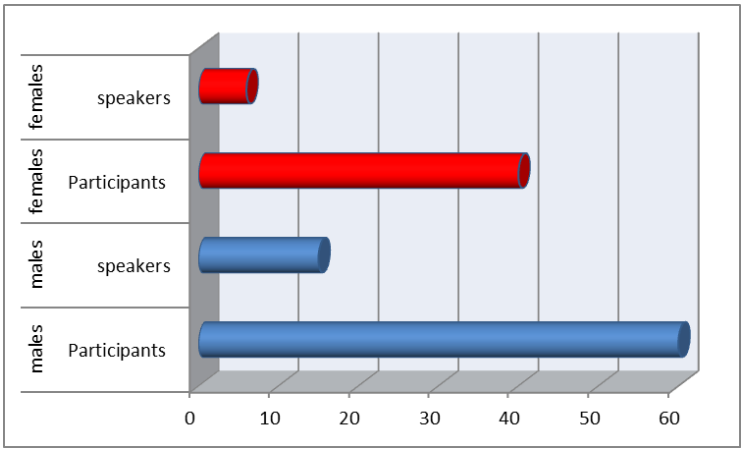


Fig 3. Gender distribution



In Italy, the System Medicine is an evolving and interesting among the clinical and research communities under a misbalance on the gender distribution a favour of males.

Overview of the results focused on:

- a better understanding of the opportunities of Systems Medicine, its importance in their daily practice and consequences for patients.
- a vision of new researches and discoveries in the field.
- possibilities to start collaborations between different stakeholders and to create networks.
- discussions about the application of Systems Medicine in Italy.
- exchanges of opinions and views.

Conclusions

It was concluded that there is a need for Systems Medicine Networks to initiate and promote interactions between researchers and clinicians who are interested in applying systems level approaches to address medical problems.

The conference primarily enabled exchanges of views and opinions among different stakeholders already working in the field, as well as those who are new to it. The attendees and participants were informed about a wide spectrum of initiatives and possibilities that the field has to offer. The discussions contributed to raising awareness about the opportunities which Systems Medicine can offer in daily clinical practice and the consequences for patients.

The main goals achieved:

1.- practical information was given on how to set up Systems Medicine approaches in clinical practice (e.g. organisational aspects, data management and data integration, lab techniques, modelling and bioinformatics) and examples of collaboration, connections with cell biology and experimental model systems.

1.- 89 people attended the event, besides the 21 speakers (including those giving welcome speeches and presentations and chairpersons).

2.- The Ministry of Health illustrated their official social media platform, the Biomedical Research Workflow Management System which was designed and developed by the Department of Public Health and Innovation, General Directorate for Scientific and Biomedical Research and Vigilance on the Institutions, Italian Ministry of Health. This system is a web-based information system that is used to manage the scientific and administrative activities related to National Research and aims at creating a National Biomedical Research Database.

Currently the system is used by more than 15,000 researchers from: 48 Scientific Institutes for Research, Hospitalization and Health Care (IRCCS); 10 Zooprophilactic Institutes (IZS); 21 Regions and Autonomous Provinces, the National Agency for Regional Health Care Services (AGENAS); the National Institute for Occupational Safety and Prevention (INAIL); the National Institute of Health (ISS).

The turn out to our event exceeded our expectations - scientists, clinicians, students, representatives from industry and policy makers attended this meeting (most of them were from research hospitals).

We received very good feedback from the participants who found the Conference very interesting, and felt that it encouraged cooperation between experts in different fields and provided an overall view of Systems Medicine.

In Italy, Systems Medicine is evolving among clinical and research communities. In addition, many participants expressed their interest in a follow-up event in Systems Medicine and in the possibility to participate in ERACoSysMed calls.

Future events could be organised specifically for junior scientists and medical students regarding the Importance of introducing Systems Medicine topics into Medical school curricula and future orientations. More possibilities for networking would be welcomed. Exchanges of opinions and views of the different Systems Medicine approaches and opportunities in daily clinical practice and consequences for the patients.

Speakers

Giovanni Apolone - IRCCS Foundation National Cancer Institute, Milan.
Giovanni Apolone, MD with post-doctoral degrees in Internal Medicine and Pharmacology, is currently the Scientific Director of the IRCCS Foundation National Cancer Institute of Milan and, previously, Scientific Director of the Institute for the Advanced Technologies and Clinical Pathways in Oncology, a Public Research Hospital, in Reggio-Emilia (Italy). He was listed as an Italian expert in the official EMA list from 2000-2007. He spent his sabbatical leave (2002) at the SENDO (Southern Europe New Drug Office, Milan, Italy) and at the FDA (Bethesda, USA). His main fields of interest are: methodological, ethical and regulatory aspects of clinical research, with a special emphasis on oncology and anticancer drugs, healthcare evaluation, health outcomes assessment (patient self-reported health status), development and validation of case-mix measures, education and health promotion research and programs.

Stefano Bonassi - Department of Human Sciences and Quality of Life Promotion, San Raffaele University and the Clinical and Molecular Epidemiology Unit, IRCCS San Raffaele, Pisana, Rome.
Stefano BONASSI, Professor of Hygiene and Preventive Medicine at the San Raffaele University in Rome, is interested in the use of biomarkers in human population and clinical studies. He coordinated the epidemiological part of large international projects, such as the ESCH on chromosome aberration, the HUMN and HUMNxl on the micronucleus assay, and ComNet on DNA damage. His current interest includes neurodegenerative disorders, COPD, aging, pharmacoepidemiology, rehabilitation.

Alfredo Cesario - IRCCS Agostino Gemelli University Polyclinic.
Alfredo Cesario is a medical doctor with a specialization in thoracic surgery and a member of the Joint Consultation Table with the Ministry of the health. He is also a consultant for the Director General of research for the Ministry of Health, a Member of the European Forum of Good Clinical Practices in Brussels, Scientific and Political Consultant of political strategies on research international, Scientific Director at the San Raffaele Institute in Rome, Member of the ethics committee and coordinator of the rehabilitation pneumology area. He has been a national expert for the Research and Development DG since 1999 and is a Speaker at major congresses and conferences at European and international level in Oncology Clinics (American Society of Oncology Clinics-ASCO), Oncology of Base (American Association of Cancer Researchers-AACR), Thoracic Surgery (Association American thoracic surgery - AATS and the European Cardiothoracic Surgery Association - EACTS, European Society of Thoracic Surgery ESTS) and Respiratory Medicine. He is Professor of pediatric surgery at the Catholic University of Rome and holds courses in cardiovascular physiology and thoracic surgery at the same location. He is an expert supervisor for the following scientific journals: "Chest", "The Lancet Oncology", "The European Journal of Cardiothoracic Surgery", "The Annal of Thoracic Surgery"

Bruno Dallapiccola - IRCCS Bambino Gesù Paediatric Hospital.
Prof. Bruno Dallapiccola is a medical geneticist, the Scientific Director of the Bambino Gesù Children's Hospital (OPBG), Italy's main paediatric Health Care and Research Institution. He was Professor of Medical Genetics from 1979 to 2009 (Urbino University, Tor Vergata and Sapienza Universities in Rome), Director of the School of Specialization and of PhD in Medical Genetics at the Sapienza University of Rome from 1999 to 2009, Director of the Unit of Medical Genetics at the Forlanini Hospital and at the Umberto I Polyclinic in Rome, Scientific Director of the Health Care and Research Institution 'Casa Sollievo della Sofferenza' in Foggia, from 1991 to 2009. He chaired the Mendel Medical Genetic Institute in Rome from 2000 to 2009. He has been President of the Italian Medical Cytogenetics, Medical Genetics, and Human Genetics Societies as well as member of the Board of Directors of the European Society of Human Genetics. From March 2013 until May 2018 he was coordinator of FP7 project "MD–Paedigree - Model-Driven European Paediatric Digital Repository" (GA n° 600932), funded in 2012 under the Virtual Physiological Human area of ICT Theme. He is member and representative for the Italian Ministry of Health of the Commission Expert Group
on Rare Diseases (formerly European Union Committee of Experts on Rare Diseases - EUCERD). He is member of the National Health Council and of the National Bioethics Committee. Since 2017 he has been member of the Pontifical Academy for Life. He is also the person responsible in Italy for the Orphanet project, the most important database for rare diseases at worldwide level. He is member of the Orphan-Europe Academy and of several scientific societies. He has published 870 papers on peer reviewed journals related to medical genetics, the identification of new diseases, the study of genotype-phenotype, mapping and cloning of over 50 disease genes, mainly related to rare and very rare diseases.

Alberto Felice De Toni - Rector of the University Udine.
Alberto Felice De Toni [Curtarolo (PD), 1955], is Rector of the University of Udine and General Secretary of the Conference of Rectors of Italian Universities. He is Professor of Economics and Management Engineering and teaches 'Organization of Production and Management of Complexity' in the Management Engineering degree course and holds lessons in various Italian Business Schools. He graduated in Chemical Engineering and did a PhD in Industrial Innovation Sciences at the University of Padua. He was the former Dean of the Faculty of Engineering, Chairman of the Italian Scientific Association of Management Engineering, Chairman of the National Committee of the Italian Ministry of Education, Universities and Research (MIUR) for the reorganization of Technical Vocational Education, Chairman of the Agency for the Economic Development of the Mountain regions of Friuli Venezia Giulia and Vice-chairman of the Area Science Park in Trieste. He is currently Chairman of the Internal Evaluation Body of the Italian National Institute of Health and Member of the Scientific and Technical Committee for the spread of scientific culture of the MIUR. His main areas of research are Operations Management, Innovation Management e Complexity Management. He is the author of over 300 national and international scientific publications.

Rob Diemel - ERACoSysMed, Zonmw, the Netherlands.
Dr Rob Diemel (Ph.D.) is a senior programme officer at ZonMw (the Netherlands Organisation for Health Research and Development). He initiates and manages national and European scientific funding programmes in the areas of Systems Medicine and systems biology, Personalised Medicine, alternatives to animal testing, human brain research, and biomedical Research Infrastructures. For his duties, Rob is a liaison between ZonMw and NWO (the Netherlands Organisation for Scientific Research). In European initiatives, Rob has been leading work packges in FP6 ERASysBio and FP7 ERASysAPP (systems biology), H2020 CASyM and ERACoSysMed (Systems Medicine) and FLAG-ERA II (Human Brain Project). Rob has a PhD in Medical Biochemistry and a MSc in Chemistry and was trained at Utrecht University (NL), University Clinic of Innsbruck (AT) and Sanquin (Dutch blood bank, NL).

Giuseppe Ippolito - IRCCS Spallanzani Institute for Infectious Disease.
Giuseppe Ippolito is the Scientific Director of the National Institute for Infectious Diseases (INMI) "Lazzaro Spallanzani" in Rome (since 1998) and Director (since 2009) of the WHO Collaborating Center for clinical care, diagnosis, response and training on Highly Infectious Diseases at INMI. He graduated in Medicine at the University La Sapienza in Rome in 1978, and he obtained his specialty degree in infectious diseases (1981), in Dermatology (1984) and a Masters Degree in Organization and Management of Health Institutions in 1997. Giuseppe Ippolito served as member of several National and international bodies on emerging infections preparedness and response. In the last 10 years, he coordinated 8 EU-funded projects in the field of Emerging and Reemerging infections, biosecurity, preparedness and response. He is involved, since 2005, as scientific coordinator, in international activities funded by the Italian Cooperation in foreign countries on emerging pathogens. He has published as main author more than 400 original papers, 26 books and 31 book chapters. He contributed to national and international policy development and advancement of public health agenda on preparedness and response of infectious diseases with epidemic potential.

Nikole Kerlero De Rosbo - Researcher Genoa University.
Researcher working in the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Science (DINOGMI), He works is centred on the analysis using molecular biology techniques and cytofluorimetira of the in vitro and ex vivo effects of experimental immunomodulatory therapies on the immune system cells of patients with multiple sclerosis. Immunological monitoring, analysis of research data, preparation of scientific papers and related projects.

Fabrizia Lattanzio - IRCCS INRCA Geriatric Hospital Ancona.
Fabrizia Lattanzio works at I.N.R.C.A. - National Institute of Rest and Care for the Elderly – and is theScientific Director. Her main duties and responsibilities are to coordinate, promote and manage the scientific activity of the Institute. She has studied indicators for measuring the quality of care for the elderly in both hospital and out-of-hospital facilities. Her fields of interest are multidimensional evaluation (VMD), models of care for the frail elderly, geriatric medicine epidemiology and pharmacoeconomics. During her professional activity a particular competence was acquired on the definition of information and IT support for research and assistance in the geriatric field.

Giovanni Leonardi. Director General For Research And Innovation In Health Care. Ministry of Health.

Massimo Locati - Head Leukocyte Biology Lab. IRCCS Humanitas, Milan.
Massimo Locati graduated with top marks in Medicine from the University of Milan (1992), was Research Fellow in the Department of Immunology and Cell Biology at the Mario Negri Institute, Milan (1992-1995) and then moved to the Laboratory of Host Defenses, National Institutes of Health in Bethesda, Washington (1995-1996). He was then enrolled as Research Assistant at the University of Brescia (1998) and subsequently moved to the University of Milan (2001), where he is now Professor of Immunology and General Pathology at the Department of Medical Biotechnologies and Translational Medicine and chief of the Leukocyte Biology Lab at the Humanitas Clinical and Reseach Center. His major scientific interests is on cellular and molecular mechanisms promoting resolution of the inflammatory response. In this scientific setting, he has contributed to the characterization of biological properties of chemokines and their receptors and in particular has first revealed the decoy function and the underlying molecular mechanisms of atypical chemokine receptors. He has also first described the transcriptional profile and characterized several immune and metabolic aspects of alternatively activated macrophages. He has also described the role of transcription factors and epigenetic mechanisms, with particular relevance for microRNA, in macrophage biology. On these topics he is author of over 130 peer-reviewed publications, with a total Impact Factor 850, 12000 citations, h-index 51 and i-10 index 101.

Christian Pristipino. Past president Italian Association of Medicine And Systemic Health (ASSIMMS)
Christian Pristipino graduated in Medicine and specialized in cardiology. He is Coordinator of the personalized care unit and medicine based in the San Filippo Neri Hospital Complex in Rome. He is Fellow of the European Society of Cardiology and the American College of Cardiology. He is responsible for research and training, in addition to the clinical activity in Italy, he deals with the management of complex pathologies , research into systems medicine, the design of complex networks of acute infarction care at the regional level of the international database creation for the sharing of clinical data patients and research of psycho neuro endocrinology in cardiology.

Jose Roca - Department Pulmonary Medicine. Barcelona University, Spain.
Prof. Dr. Josep Roca Torrent is Professor of Medicine at the University of Barcelona, senior consultant at Hospital Clínic of Barcelona and senior researcher at IDIBAPS, as well as Adjunct Professor at the University of Southern Denmark (Odense). Author of more than 300 original articles in peer-reviewed journals and several book chapters, review articles and books. His two main fields of interest are: Chronic patients management (integrated care and systems medicine) and gas exchange and skeletal muscle bioenergetics in chronic respiratory diseases.

Damjana Rozman - Faculty of Medicine. University of Ljubljana, Slovenia.
As a full professor and Head of the Centre for Functional Genomics and Bio-Chips (CFGBC) at Faculty of Medicine University of Ljubljana, D. Rozman engages in systems medicine research (multifactorial liver pathologies) and also in undergraduate/graduate education. She coordinated the training activities within the FP7 Coordinated action CASyM and participated in training within the FP7 infrastructure grant ISBE. She was among founding members of the European Association for Systems Medicine (EASyM) and is currently a member of the Management Board responsible for education and training. She is also the Slovenian scientific representative in the Management Board of the ESFRI infrastructure ELIXIR.

Harald Schmidt - Department Pharmacology & P.M. F. Health. Maastricht University, NL.
With a double degree in Medicine and Pharmacy, Harald Schmidt has a passion for systems medicine, i.e. to re-define what we call "disease" from a descriptive symptom-based to a mechanism-based approach by using big data, innovative target validation and rapid repurposing of registered drugs for new clinical applications. As an ERC Advanced Investigator he performs high risk/high potential benefit research in areas of major medical need, such as another ERC funded a proof-of-concept grant to develop and commercialise a first-in-class neuro-protective therapy in stroke. He chairs the COST action OpenMultiMed contributing to the Big Data-based evolution of Medicine and coordinates the H2020 project REPO-TRIAL. His multi-national research experience in Academia and Industry has led to high impact publications (Hirsch 83) with high socio-economic relevance such as patents, biotech spin-offs and patient benefit.

Marco Salvatore - Rare Disease Center. Italian National Institute Health, Italy.

Marco SALVATORE, biologist, specialized in molecular Applied Genetics, Cytogenetic and Molecular Genetics, Researcher of the National Center for Rare Diseases (ISS). He studies the role of microRNA in rare diseases; rare diseases epidemiology; hepatoblastoma; multiple exostosis; Hailey-Hailey disease; correlation between specific rare diseases and Oxidative stress. From 2016 he is Member of the Scientific Committee of the Italian Cystic Fibrosis (CF) Patients Registry. From 2014 he is member of the Undiagnosed Rare Disease International Network (http://www.udninternational.org/home) and of the Undiagnosed Rare Disease National Network (http://www.udnpitaly.com/). He is involved in the management of national and international project. He is member of the Italian project for external quality assessment of sweat test for cystic fibrosis coordination team (http://www.ceqtestdelsudore.it/). He attended at the Management Board of the European Molecular Genetics Quality Network (alternate Domenica Taruscio from 2004 to 2015).

Michael Steffens - Research Division, Federal Institute Drugs and Medical Devices, Bonn, Germany.
Dr Michael Steffens is a physician and computer scientist and heads the genetic bioinformatics in the research division at the Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany. He has many years of internationally proven experience in the fields of genetic epidemiology, bioinformatics and pharmacogenomics. Current fields of interests are the evaluation of high-throughput data, statistical-pharmacogenetic data modelling and software programming, and the application of machine learning techniques in the analysis of heath care data.

Fabrizio Tagliavini - IRCCS Neurological Institute Carlo Besta.
Dr. Taglavini is a neurologist and neurophatiologist. Currently he is the Scientific director of the IRSCC Foundation Carlo Besta Neurological Institute (Milano,I) and President of the Italian Network of the IRCCS-Research Hospitals of Neuroscienze and Neurorehabilitation. He is a member of international bodies, including the Management Board of JPND and the Scientific Advisory Board of ERA-Net NEURON. His research is focused on degenerative dementias due to protein misfolding.

Elena Tremoli - IRCCS Monzino Cardiological Center.
As Scientific Director of the IRCCS Monzino Cardiological Center and President of the IRCCS Cardiology Network, her scientific interests are related to cardiovascular diseases with the specific aim of identifying novel diagnostic and prognostic markers, and risk factors of atherosclerosis, thrombosis and inflammation. The combination of new technologies and techniques offers the potential for refined, targeted approaches toward cardiovascular precision medicine.