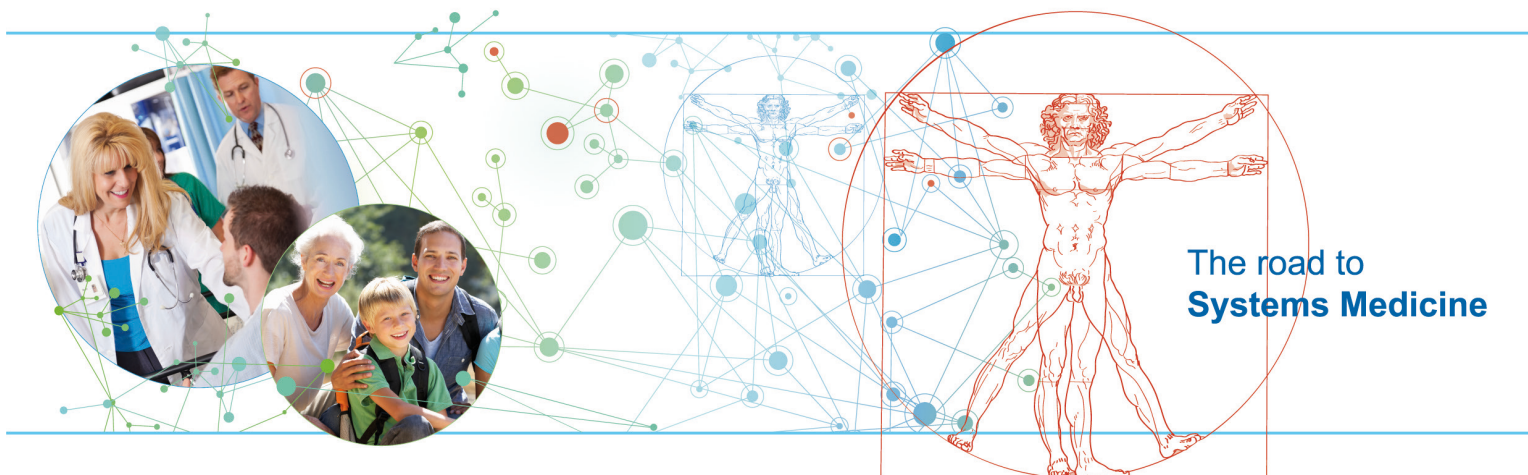




THE CASyM ROADMAP

Implementation of Systems Medicine across Europe

IMPRINT

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Preamble

The need for a new concept in medicine

By David Harrison

The nation states of the European Union face unprecedented challenges as a result of an ageing population, re-emergence of infection as a global threat, increased needs for social care and a growing burden of curing and caring for patients with cancer. As well as the health of European citizens being at stake there is a huge economic challenge in making rapid, affordable and effective interventions widely available.

The concept of P4 Medicine has grown in stature; encompassing personalised, predictive, participatory and preventive medicine. Most emphasis has perhaps been put on personalised medicine, because it is so readily understood and because success should, in theory at least, be easy to measure. However, it would be a mistake to believe that personalised medicine alone can meet all the needs of Europe's health economy: the development of new drugs for cancer, cardiovascular disease and dementia must be made faster, cheaper and more effective before personalising them: the design of effective interventions, for example to control obesity, needs some method to predict and choose the best intervention, rather than having to wait for 10 or 15 years to assess outcomes. Participation of patients in health must be more fundamental than simply personalising medicine; it must be about empowering citizens to be responsible and engaged in protecting their own health and the health and well-being of the communities where they live and work.

Research has thrived; technology has revolutionised laboratory, clinical and community based research; data abounds, but we urgently need to be able to take this data and render it into information that is useful for personalisation of medicine, prediction of new interventions that will work, participation of citizens in taking responsibility for their own health, and design

and implementation of efficient preventive measures to preserve wellbeing based on rationally designed strategies.

The need is pressing to implement methods and approaches, and in particular to fill the deficit between data generation and storage and real impact in the clinic and community. We have had a revolution in the generation of data; we need a revolution in using that data to drive forward health.

The roadmap to Systems Medicine offers the means to that end; to change how we engage our citizens to use data of both the healthy and unhealthy; to think about prediction and prevention; and ultimately to improve the lives of individuals. Already progress has been made, for example in development of predictive tests that allow the personalisation of new anti-cancer drugs, but arguably this is personalisation for a disease type rather than a person, and this incremental, case-by-case approach will become unaffordable for the really big challenges that face us.

When discussing Systems Medicine a common question is its definition. Is it simply systems biology applied to medicine? Is it an overarching term to describe the advent of high throughput -omics, the era of functional genomics? Does it require computational modelling; are we trying to model in silico what will happen in real life? Is it static or is it dynamic, recognising that the course of patient's life changes, and that disease itself changes and adapts over time?

Our response is that whilst we can define it as an academic subject, it is much more important to appreciate that systems medicine is an approach, a way of thinking, a conceptual framework, focussed on outcome and impact rather than as a theoretical discipline. A roadmap is intended for use when the intended destination is known: it describes a route, or possibly several different routes, to arrive at the destination. Perhaps just as importantly, a good roadmap allows the traveller to join or leave the highway at different points: some journeys may be short and simple, whilst others may be full expeditions

requiring extensive preparation, commitment and expense. But, whatever the destination, the roadmap should be consulted when the roads are new and scarcely travelled.

So rather than being prescriptive, the CASyM Roadmap for Systems Medicine is an invitation to citizens, policy makers, funders, scientists, clinicians and industry to specify a destination and set out on a journey with a new over-arching conceptual framework to turn information into action, to inform future of healthcare and medicine, drawing upon the participation of the healthy and unhealthy, to prevent disease in populations as well as individuals, to predict the effectiveness of drug development and improve drug

trials and other therapeutics interventions, and to truly personalise medicine to the needs of a person, not just a disease. Are there success stories? Already the answer is yes, but increasingly as the principles of integrating data are adopted the success will not be measured by single projects but an increasing momentum of effective translation of research into practice, which in turn will influence research. For some projects the road may be joined for just a short time, for other destinations the journey may be long and hard, but the roadmap serves to give a direction of travel, emphasising the opportunities by integrating the very best of new skills and tools from all sorts of disciplines for the common good.

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The CASyM roadmap: Implementation of Systems Medicine across Europe



Abbreviations

CASyM	Coordinating Action Systems Medicine
CME	Continuing Medical Education
CPD	Continuing Professional Development
EC	European Commission
ECTS	European Credit Transfer System
EMR	Electronic Medical Records
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
EU FP6	European Union Sixth Framework Programme
FDA	US Food and Drug Administration
IMI	Innovative Medicines Initiative
mRNA	Messenger ribonucleic acid
PD	Pharmacodynamic
PK	Pharmacokinetic
PPP	Public Private Partnerships
RNA	Ribonucleic acid
SILM	Professional Education for Laboratory Medicine
SME	Small and Medium Enterprise
SNP	Single-nucleotide polymorphism
P4	Predictive, Preventive, Personalized and Participatory (Medicine)

Executive Summary

Why is Systems Medicine needed?

Healthcare today faces a variety of challenges associated with highly variable treatment efficacies of drugs on the market, ineffective prescriptions¹ and a reactive rather than proactive approach in treating disease. This results in a huge cost burden of the healthcare systems. The reasons for why we have not yet overcome these challenges are manifold, but most importantly lie in the intrinsic complexity of the human body and the diseases it develops. Human disease can be perceived as perturbations of multifaceted, integrated genetic, molecular and cellular networks in combination with influences from environmental factors. These interactions are multidimensional over time and space and may also vary in subgroups of patients that appear to have the same diseases. This underlying complexity necessitates a new approach to handle the challenges associated with disease. But in addition it also requires new ways of thinking about maintaining a healthy life style.

Systems Medicine can be viewed as a new concept added to the clinical toolbox which will significantly benefit the daily lives of medical practitioners and patients through an integrative approach to understand. However, its most effective impact will be derived from a change in the mind set and workflow of biomedical research and medical care. The vision of this European roadmap is to develop Systems Medicine into a practical framework that assists clinical decision making and the design of personalised prevention and treatment plans. It is akin to the changes that avionics, heads-up display and fly-by-wire have made to modern aviation. Systems Medicine will give tools that will help to manage a person's health as well as patient's disease

but it will also provide a wealth of real time information and interpretative control systems that increase both safety and efficiency.

Systems Medicine employs a truly integrated approach which holds huge potential for a more comprehensive understanding of human health and disease. Building on advances in systems biology, this approach fuses the disciplines which currently found medicine (biology, physiology, pathology, pharmacology, epidemiology and therapeutics) together with informatics, computer science, mathematics, physics, and engineering. The power of this fusion is exploited through the development of computational models which can enable researchers to map the (mal)functioning of the human body, its processes and interactions across multiple levels of structural and functional organisation -from molecular reactions, to cell-cell interactions in tissues, to the physiology of organs and organ systems. These approaches are already laying the foundation for a medical practice that is increasingly predictive, preventive, personalized, and participatory, and have the potential to lead to beneficial economic and social impacts through the targeted application of therapeutics and preventative measures.

This roadmap, the result of a broad cross-disciplinary stakeholder consultation process, identifies four core priority actions (community building, proof of concept/pilot study, cross-disciplinary training and data access, sharing and standardisation) and ten key areas necessary to the successful implementation of Systems Medicine in Europe. These areas, including patient stratification, the design of clinical trials, and clinical data access, -sharing and -standardization, involvement of industry, development of the necessary technical infrastructure and the provision of multidisciplinary

¹ What happened to personalized medicine? Nature biotechnology 2012, Editorial ([PDF](#))

training, are outlined along with cross-cutting priority actions and specific recommendations over a period of 2, 5 and 10 years.

The roadmap asserts that investment in proof of concept/pilot studies will help to precipitate a paradigm shift in the way medicine is practiced. This shift will be supported by a strong Systems Medicine community, new multidisciplinary training programmes and the

development of new European-wide practices in clinical data access, sharing and standardisation.

By building on current national and international efforts in Systems Medicine, and the coalescing of the many stakeholder groups, it is anticipated that this coordinated action will bring significant and sustained benefits to the European citizen, both in sickness and in health.

A paradigm shift toward implementing Systems Medicine

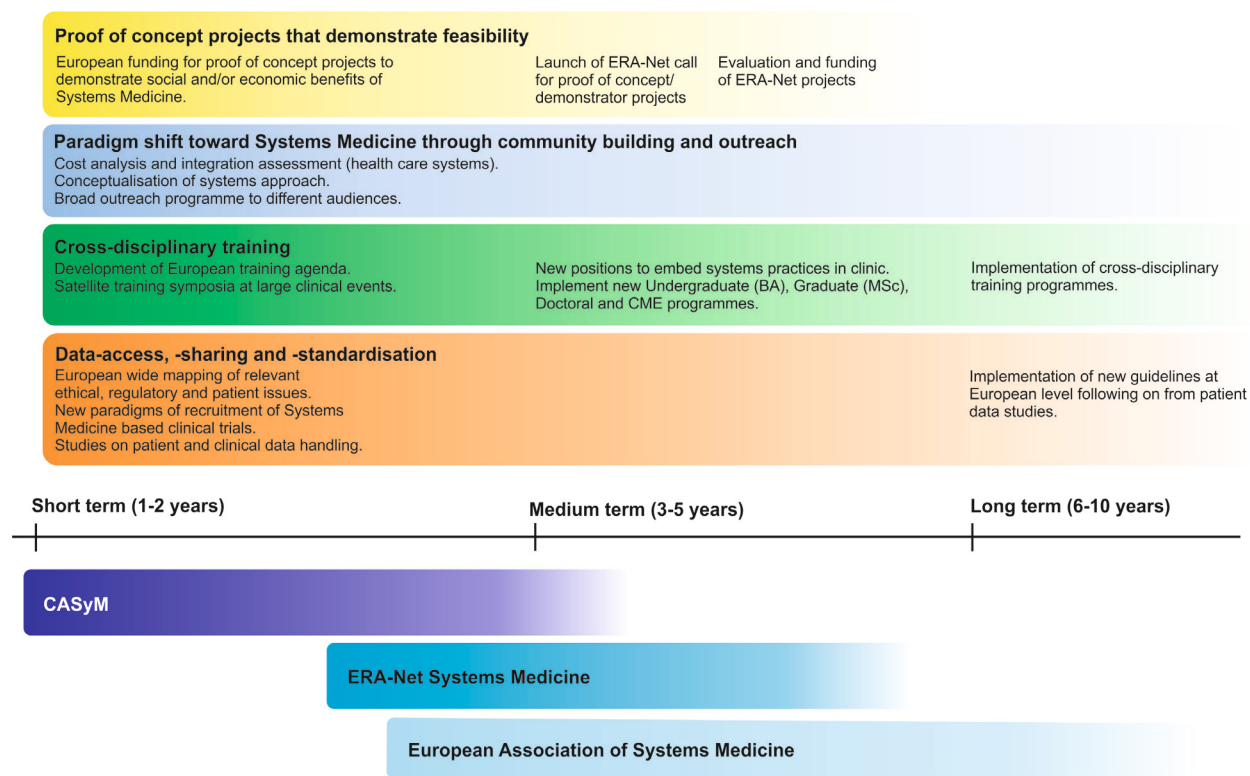


Figure 1: A pragmatic view to implement Systems Medicine in the short, medium and long term.

The required changes to build a sustainable framework for the implementation of Systems Medicine cannot be reached in one step. While some steps can be taken in parallel, each step needs to be warranted by the preceding step in order to ensure an organic progression that will change the system from within (for further details see section *Implementation strategy for Systems medicine* and table 1). The guiding principle is a pragmatic view to establish Systems Medicine approaches in the short, medium and long term. Such an approach will provide a new tool to clinicians that will step change the capabilities of the clinician to diagnose and treat patients faster, better and more effectively – a tool, which has the potential to become a generic prerequisite for any personalized or P4 medicine approach. Therefore, the current roadmap aims to formulate implementation goals over short, medium and long term timeframes as described in detail in the following sections of this document. *Upper half:* Investment in proof of concept, training programs and adapted data handling methods are needed to initiate a paradigm shift towards a medicine that is increasingly predictive, preventive, personalized and participatory. Systems Medicine is the most promising approach to reach this goal (see table at the end of this chapter for more details), thereby driving the needed paradigm shift. *Lower half:* Accompanying initiatives and projects that initiate fuel and sustain the implementation of Systems Medicine across Europe. CASyM: see this document; ERA-Net Systems Medicine: Newly applied ERA-Net, based in part on the current document and currently under review; European Association of Systems Medicine: The founding of such an association is currently under review by the CASyM consortium.

Roadmap report

Background

A new paradigm in healthcare

Systems Medicine is the patient-oriented concept of medical research and practice of the next decade, integrating multiple disciplines including mathematics, computer science, data analytics and biology as well as clinical medicine, ethical and societal issues. The comprehensive appraisal and analysis of individual patient data that Systems Medicine enables will lay the grounds of a more predictive, preventive, personalized and participatory P4 medicine^{2 3}. Major advances in biotechnology, harnessed by Systems Medicine, will enable medical practice to manage a person's health, instead of managing a patient's disease. By applying new computational and mathematical tools to medical practice, we can move from a largely reactive mode of medicine to one that is more focused on wellness and is more cost-effective. This is no small challenge, and there are considerable hurdles that must be overcome, from changing medical working practices entrenched over decades to developing the necessary technical infrastructure. The benefits, however, are significant:

Predicting and Preventing: Researchers are increasingly realising that our bodies cannot be subdivided down into independent components, but rather, genes, proteins, cells and organs interact with each other and the environment in complex ways that can vary over time. Systems Medicine aims to shed new light on these interactions by integrating data from different disciplines into biological models with the power of

computer science, mathematics and engineering for the holistic understanding of health and disease. These models can, for example, assist in the detection of disease at an earlier stage, when it is easier and less expensive to treat effectively and reduce adverse drug reactions by more effective early assessment of individual drug responses. In doing so, the emphasis of medicine can be shifted from reaction to prevention, from disease to wellness.

Personalising: Medical practitioners have always considered a wide variety of factors when considering therapies for their patient, from medical history, environment to age and gender. The rise of genomics and the accumulation of multiple -omics-data and longitudinal and dense multidimensional time series, incorporated into a new systems approach, is now enabling the genetic make-up of individuals to be considered when making plans for treatment. The use of new molecular and diagnostic technologies to look at the genetic profile and biomarkers of diseases opens new pathways to match each patient with the treatment regimen that may give them the best results.

Participating: Systems Medicine brings together expertise from a spectrum of communities; its stakeholders encompass patients and medical practitioners, policy-makers, industry and researchers from disparate disciplines. The systems approach is predicated on collaboration and participation, aiming to empower individuals to become proactive co-managers of their health and wellbeing, with the confidence, knowledge and tools to manage and share their health data.

With the breadth and variety of the stakeholder groups involved in Systems Medicine comes the distinctive challenge of elucidating common goals and

² Sobradillo P, Pozo F, Agustí A. P4 medicine: the future around the corner. Arch. Bronconeumol. 2011 ([Pub Med](#))

³ Hood L, Galas D. P4 Medicine: Personalized, Predictive, Preventive, Participatory: A Change of View that Changes Everything. Computing Community Consortium; 2008 ([Article](#), [PDF](#))

shared concerns that form the basis for this roadmap. The Coordinating Action Systems Medicine (CASyM; see Annex I) represents the overarching concept and the catalyst for this process.

Why this roadmap?

To benefit from the significant potential that a holistic, systems approach to medicine can offer, it will be necessary for all stakeholders to embrace new ways of thinking and working. In order to initiate the necessary paradigm shift through a broad community building effort, the European Commission (EC) has launched CASyM, a large-scale coordinating network of scientists and physicians as well as representatives of industry and funding bodies. CASyM is tasked with formulating a European wide implementation strategy (roadmap) for Systems Medicine. The roadmap is driven by clinical needs: it aims to identify areas where a systems approach can address clinical questions and solve clinical problems.

The CASyM consortium was charged by the EC to prepare this consensus-building strategic roadmap to outline the implementation of Systems Medicine across Europe. It reflects the vision of the CASyM stakeholders (Annex I).

The aims of the roadmap are to:

1. explain the current state of the art and why we need Systems Medicine.
2. identify the challenges for and opportunities of Systems Medicine.
3. identify the stakeholders and initiate a dialogue between them.
4. provide a vision for the implementation of Systems Medicine.
5. provide examples for its application.
6. formulate reasonable and achievable goals.
7. provide a practical implementation guide for Systems Medicine.

The crucial point for a general acceptance of the Systems Medicine approach, and this proposed roadmap, is a common understanding of its breadth and clinical applicability. This roadmap aims to translate this understanding into a guide for the development and implementation of Systems Medicine.

The roadmap does not seek a prescriptive focus on specific diseases, rather it promotes any systems medical work that can show the clinical utility of Systems Medicine. To illustrate where a Systems Medicine approach can have, or already has had, a beneficial effect, a section on example disease topics and areas of medical practice has been included (see chapter 6 for more application examples).

To define or not define?

This is extensively discussed and many see a precise definition as impracticable. However, some definition is necessary because without it the task of implementing the concept for Systems Medicine becomes impossible. A useful definition is not necessarily comprehensive, but it must effectively communicate the concepts underlying the approach. The following working definition of Systems Medicine, developed by the CASyM consortium and stakeholders (see Annex I), is supported for this roadmap:

Definition of Systems Medicine

Systems Medicine is the implementation of Systems Biology approaches in medical concepts, research and practice. This involves iterative and reciprocal feedback between clinical investigations and practice with computational, statistical and mathematical multiscale analysis and modelling of pathogenetic mechanisms, disease progression and remission, disease spread and cure, treatment responses and adverse events as well as disease prevention both at the epidemiological and individual patient level.

As an outcome Systems Medicine aims at a measurable improvement of patient health through systems-based approaches and practice.

State of the art

The challenge of disease complexity

To manage the complexity of the human body and the diseases it develops, biological and medical science have tended to employ a reductionist approach, breaking down complex problems into smaller, simpler and more tractable units. However, major and chronic diseases are multifactorial in nature and reductionist biology struggles to provide solutions. Human disease can be perceived as perturbations of complex, integrated genetic, molecular and cellular networks and such complexity necessitates a new approach.

Recent developments in the life sciences have seen the coalescing of the new field of systems biology that examines the broader biological 'system' in a more holistic way. By using mathematical modelling and high-throughput tools, more complex aspects of biology can be studied. This not only includes the interpretation and integration of large-scale data (such as genomic, transcriptomic, proteomic and other '-omics' data) but also for instance the study of complex features in intracellular communication networks, which often display features that are not obvious to the human mind. Using this approach, concepts of a wide variety of disciplines such as mathematics, physics and engineering are applied to biological systems. The tools and approaches that are being developed for systems biology are beginning to make a more translational impact in the arena of medical science. There is a need for flexible, integrative systems approaches to combine such '-omics' data with clinical, societal and environmental factors including sex, type of work, sleep and eat habits that will result in medical practice that is predictive, preventive, personalized, and participatory.

Systems approaches are already making important contributions to medical practice. Success stories for medical applications showing the feasibility of systems medical approaches have already started to appear in the literature.

Some of these examples are listed below (please see Annex II for further readings):

- ▶ A generally applicable systems medical strategy to identify and validate novel diagnostic and therapeutic candidate genes⁴
- ▶ EGF receptor system stratification in breast cancer⁵.
- ▶ Heart modelling – approval by US Food and Drug Administration (FDA) for the use of a model to test new cardiac drugs⁶.
- ▶ Entelos has created 'virtual asthma patients'⁷.
- ▶ A model of CJD explaining the pathogenesis and disease progression, suggesting novel and more effective treatments for psychiatric disorders⁸.
- ▶ Chronobiological modelling of drug effects that could improve the efficacy of cancer chemotherapy⁹.
- ▶ Prediction of dementia amongst cognitively normal elderly using metabolomics¹⁰
- ▶ Combinatorial drug design to target interacting or complementary pathways¹¹
- ▶ Spatially resolved models to simulate drug distribution in the liver¹²

⁴ Bruhn et al. A generally applicable translational strategy identifies S100A4 as a candidate gene in allergy. *Sci Transl Med*. 2014 ([PubMed](#))

⁵ Wiens et al. Luminal subtypes predict improved survival following central nervous system metastasis in patients with surgically managed metastatic breast carcinoma. *Arch Pathol Lab Med*. 2014 ([PubMed](#))

⁶ Woodcock and Woosley. The FAD critical path initiative and its influence on new drug development. *Annu Rev Med*. 2008 ([PubMed](#))

⁷ Bangs. Predictive biosimulation and virtual patients in pharmaceutical R and D. *Stud Health Technol Inform*. 2005 ([PubMed](#))

⁸ Méndez and Femat. A model of CJD explaining the pathogenesis and disease progression, suggesting novel and more effective treatments for psychiatric disorders. *IET Syst Biol*. 2011 ([PubMed](#))

⁹ Lévi. The circadian timing system: a coordinator of life processes: chronobiological investigations. Implications for the rhythmic delivery of cancer therapeutics. *IEEE Eng Med Biol Mag*. 2008 ([PubMed](#))

¹⁰ Mapstone M et al. Plasma phospholipids identify antecedent memory impairment in older adults. *Nat Med*. 2014 ([PubMed](#))

¹¹ Sun et al. High-Throughput Methods for Combinatorial Drug Discovery. *Sci Transl Med*. 2013 ([PubMed](#))

¹² Schwen et al. Spatio-temporal simulation of first pass drug perfusion in the liver. *PLoS Comp Biol*. 2014 ([PubMed](#))

In the area of drug development, ‘big pharma’ has started to incorporate systems approaches to create molecular models of disease and drug action through systems pharmacology, while a number of Small and Medium Enterprises (SMEs) in the pharmaceutical sector have had success utilising a systems approach. These developments, though, are in their infancy and in a minority; Systems Medicine as an overarching framework requires broad-scale acceptance of the value of *in silico* approaches, an approach successfully pioneered in the European Union (EU) Sixth Framework Programme (FP6) NoE BioSim and STREP TEMPO. The same holds true for technology based industry for non-invasive treatment, medical devices and remote patient monitoring.

In Europe, the EC has recognised the significant potential of Systems Medicine and has, since 2004, already funded 73 health projects and allocated €415M for research, training and infrastructure in system biology. The main themes covered are addressing basic biological processes, bacteria, yeast, mammalian cells and diseases. These pioneering studies, involving an increasing number of SMEs, have led to encouraging results, globally recognized, that are propelling one of the ambitious HORIZON 2020 objectives which ultimately consists in building the European strategy for Systems Medicine (see Annex III for further details on supported projects).

Further reading:

1. *From Systems Biology to Systems Medicine*¹³
2. Vandamme et al., *Systems Medicine: helping us understand the complexity of disease*. QJM. 2013 ([Pub Med](#))

Relevance of Systems Medicine to clinicians

Systems Medicine is driven by clinical needs and real life stories, as summarised in the 2010 EC report *From Systems Biology to Systems Medicine*¹³. Clinicians have been engaged from the outset of the development of this road map, and will be key players in the future development of Systems Medicine. They will be critical to identifying the clinical challenges and unmet clinical needs that will benefit from Systems Medicine approaches.

Systems Medicine can be seen as a natural extension of clinical decision-making. These are built on pattern

recognition and reasoning about causality. Systems Medicine provides methods to integrate multiple layers of molecular and clinical data in formats that allow understanding of disease mechanisms as well as diagnostic prediction. The main differences with the current clinical decision approach are that Systems Medicine enables higher resolution and computational predictions, incorporating the ever increasing volume and complexity of data, such as genome sequences, into decision-making. Failure to tap this seam of information denies medicine an enormous amount of patient and disease relevant information.

Changes in clinical practice are often introduced through clinical trials. Thus, this road map will outline how the Systems Medicine approach will change the design and delivery of clinical trials. The aim of a greater personalising of medicine suggests more clinical trials with more patients, which is unsustainable using current approaches. However, by employing advanced statistics and computational modelling of patient responses in adaptive trials, Systems Medicine approaches enable more conditions to be tested per trial, reducing the number of patients and time required.

Systems Medicine offers a systematic and tractable approach to the challenges faced by clinicians that is reproducible, scalable and evolvable. Systems Medicine will provide new tools that will step change the capabilities of the clinician to diagnose and treat patients faster, better and more effectively. It is a new conceptual approach and this is why we expect it will change patient outcomes. In the medium and long term, the success of Systems Medicine will be measured by new biomarkers, new devices (strongly facilitating doctor/patient interaction), novel drugs and patient management strategies. Thus, Systems Medicine offers the concept to make a significant impact on clinical practice and patient outcomes.

Harnessing computational, statistical and mathematical tools to analyse and interpret biomedical data

In principle, there are two important analytical strategies in Systems Medicine, namely those that are either network- or modelling-based:

Network-based strategies: Common diseases involve altered interactions between thousands of gene

¹³ From Systems Biology to Systems Medicine – Workshop ([PDF](#))

products, metabolites and environmental factors. Single biomarkers will therefore not suffice to achieve P4 medicine. High-throughput, ‘-omics’ technologies allow simultaneous analyses of most known gene products and metabolites. However, interpreting the data is a great challenge. Network-based analyses of ‘-omics’ data from patients play a key role. Briefly, networks provide graphical representations of complex systems. In the context of cellular networks, molecules such as genes and proteins are represented as nodes, and the interactions among them as links.

In 1999 Barabasi and Albert¹⁴ showed that networks in a wide variety of technological, social, and biological systems have common designs that are governed by simple and quantifiable organizing principles. An important characteristic was that functionally related nodes tended to be highly interconnected and co-localized in the networks, thereby forming *modules*. Such modules have important clinical indications. Modules may help to organize and prioritize between the many disease-associated genes identified by high-throughput analyses, as well as to get an overview of disease-mechanisms by performing pathway analyses. There are several successful examples of module based strategies to find biomarkers and therapeutic targets in inflammatory and malignant diseases^{15, 16, 17, 18}.

Modelling based strategies: Modelling is an analysis tool that allows one to study the mechanisms and properties of a system, formulate new hypotheses and extract rules that can make predictions about future behaviour¹⁹. Thus, while no model can explain everything, good models can solve questions, guide empiric experimentation, and assist in decision-making²⁰. A large number of different mathematical,

statistical and computational tools are being used in systems biology.

Commonly used methods include:

- ▶ Clustering and classification
- ▶ Data driven modelling
- ▶ Dynamic deterministic methods
- ▶ Statistical models and regression analysis
- ▶ Rule-based and logical models
- ▶ Flux and control analysis

In order to harness these rich theoretical tools for life sciences and medicine a question or hypothesis has to be formulated that can be answered based on the data and information available. The theoretical methods are best viewed as analysis tools that help to organise, explain and interpret data. As with any analytical tool, they only will work on data of adequate quality, quantity, density and structure. Similarly, they have certain limitations or biases, they are sometimes used in combination or hybrid approaches.

Grand challenges for modelling approaches in Systems Biology and Systems Medicine are²¹:

1. *Methods:* To devise new theoretical methods that are more powerful in extracting the information contained in the currently available data. In particular, we have to develop methods that can mine and interpret high throughput ‘-omics’ data.
2. *Integration:* To develop methods for the integration of different data types, such as molecular data, physiology data, imaging data, clinical data and personal patient data.
3. *Modelling:* To develop truly multiscale modelling methods that can seamlessly model across different anatomical scales, i.e. from intracellular processes to cells, organs, organisms, and populations.
4. *Data:* To develop approaches for utilising data from electronic medical records (EMRs) and data from connected health devices and integrated health ITC-based systems.
5. *Experiments:* To identify gaps in data provision, and in collaboration with data generators devise approaches

¹⁴ Barabasi AL, Albert R. Emergence of scaling in random networks. Science. 1999 ([PubMed](#))

¹⁵ Bruhn S et al. A generally applicable translational strategy identifies S100A4 as a candidate gene in allergy. Sci. Transl. Med. 2014 ([PubMed](#))

¹⁶ Lee JC et al. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. J. Clin. Invest. 2011 ([PubMed](#))

¹⁷ Jörnsten R et al. Network modeling of the transcriptional effects of copy number aberrations in glioblastoma. Mol. Syst. Biol. 2011 ([PubMed](#))

¹⁸ Chen N et al. Cancer metastasis networks and the prediction of progression patterns. British J Cancer 2009 ([PubMed](#))

¹⁹ Wolkenhauer O. The role of theory and modeling in medical research. Front. Physiol. 2013 ([PubMed](#))

²⁰ Wolkenhauer O. Why model? Front. Physiol. 2014 ([PubMed](#))

²¹ Wolkenhauer O et al. Enabling multiscale modeling in systems medicine. Genome Medicine 2014, 6:21 ([web link](#)).

to improve experimental design and optimise data generation for use in modelling approaches.

6. *Clinical paradigms*: To propose novel clinical paradigms for diagnosis, treatment, patient care and prevention, that will change current medical practice and health care systems
7. *Education*: To educate the users and to enable them to make more competent decisions.

The establishment of useful models for Systems Medicine requires the close and iterative interaction between clinicians, experimentalists, and theoreticians.

To establish these interdisciplinary consortia, we will need to:

1. *Evolue*: Change the current view of clinicians towards modelling by demonstrating successful proof of concept studies.
2. *Integrate*: Encourage theoreticians to engage with clinicians and experimentalists to tackle biomedical and clinical problems that are not easily tractable.
3. *Provide tools*: Develop user-friendly bioinformatic and mathematical tools to integrate and interpret network-based and multidimensional sets of data to address the complexity of patients. Prerequisite for a successful handling of such data sets are consistent sampling methods and standards across Europe and computational/mathematical models that are as close as possible to the *in vivo* situation of the patient.
4. *Work on expert systems*: Develop a new generation of expert systems (expert systems are computer systems that can emulate the decision-making ability of a human expert) that can assist the clinical practitioner in making decisions based on multidimensional inputs that transcend human combinatorial thinking due to the sheer amount of data (e.g. genome sequences). Continuous high quality updating of these expert systems is essential. This field has the potential to have very direct involvement in the everyday clinical activity. These new generation expert systems could address the vast complexities and variations of individual patients' pathologies, thereby changing the current practice of medicine towards systems thinking.

While large and long-term research initiatives, like the Virtual Physiological Human, the Human Brain Project or IT Future of Medicine (however, not funded as EU

flagship project) are aiming to develop comprehensive, computational representations of organs and organ systems, this road map focuses on opportunities for smaller, interdisciplinary collaborations between clinicians and modellers targeting specific questions of clinical relevance.

Mathematical modelling provides a conceptual framework to guide the interpretation of data, generated from complex biological systems. More important than numerical predictions, is the process of modelling as a way of thinking about complex systems, to critically assess the relevant system variables and their interactions, to reveal the dominant biological processes underlying observed dynamics, to limit outcomes to plausible ranges and to highlight uncertainties²².

Recommendation

To tackle these challenges, an EC requirement to give access to data and data sharing as prerequisite for the evaluation of proposals is recommended. The EC can play a central role in opening up necessary and needed channels of information.

²² Epstein JM. Why Model? Journal of Artificial Societies and Social Simulation. 2008 ([web link](#))

Implementation strategy for Systems Medicine

The ten key areas for a successful implementation of Systems Medicine

This section provides a summary of the main challenges and opportunities for the implementation of Systems Medicine in Europe, extracted from various CASyM events and workshops. Further detail on these issues is provided in Annex VII: Reports from stakeholder events and workshops.

Ten key areas have been identified of consideration for the successful implementation of Systems Medicine in Europe (Fig. 2).

Cutting across these ten key areas are the requirement for a *paradigm shift* in the way healthcare is operated in Europe; the *building of a strong community and outreach programmes*, the development of *proof of concept* success stories in Systems Medicine to improve understanding and show the utility of the approach; *training and education programmes* to embed systems approaches; and a Europe-wide consensus on issues relating to *data access, sharing and standardisation* (see also Fig. 1).

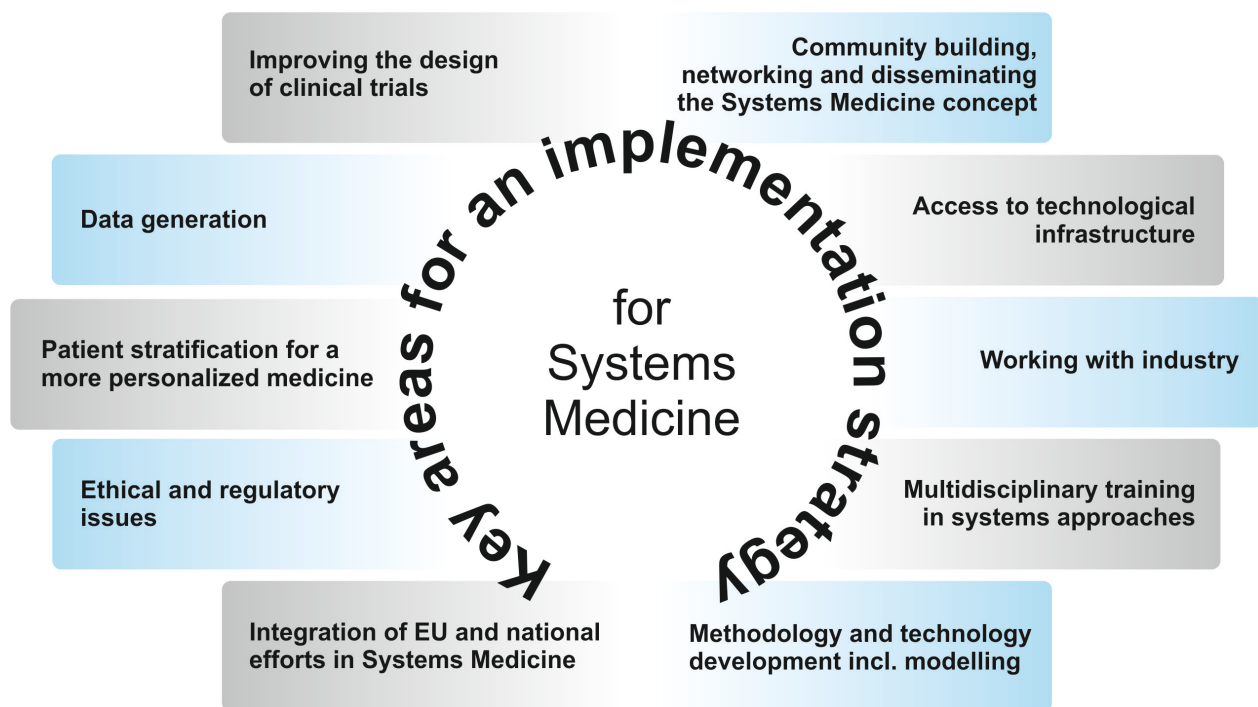


Figure 2: Key areas for a successful implementation of Systems Medicine across Europe.

I - Improving the design of clinical trials

This is an abridged version of the roundtable discussion on clinical trials at the first CASyM stakeholder conference, March 2013. The link to the full report can be found in Annex VII of this document.

Systems Medicine shows significant potential for disruptive changes resulting in enhanced design and execution of clinical trials. The challenges are not insignificant. A paradigm shift will be required to initiate the wholesale redesign of clinical trials which will favour a patient-oriented approach, one that targets pathways and factors in co-morbidities. Changes to current inflexibility of trial design to favour adaptability.

Currently, a lack of high-quality, accessible and standardised datasets hampers researchers' capacity to utilise the large volume of '-omics' data being produced. Finally, the need for categorization of existing, deterministic and probabilistic modelling approaches was also identified as a low-impact but highly needed modality of action to foster the progress for a Systems Medicine approach to clinical trials.

Major impacts can be anticipated in four key areas:

1. Optimization of drug discovery and design in pre-clinical phases
2. Disruptive re-design of Phases I and II
3. Deployment of systems level pharmacodynamic measures from discovery through development
4. Convergence between Coordinated Care across healthcare tiers and Systems Medicine should lead to profound changes in Phases III and IV that will likely disappear as conceived today.

2 - Methodology and Technology development including modelling

This is an abridged version of the report *The Role of Multiscale Modelling in Systems Medicine*, June 2013. The link to the full report can be found in Annex VII of this document.

Defining methodologies for data analysis, modelling and simulation for multi-scale modelling in a clinical context: Over the last decade, we have gained detailed insights into the structure and function of molecular, cellular and organ-level systems, with technologies playing an important role in the generation of data at these different scales. An important (and challenging) theme for Systems Medicine is the *integration* of this knowledge across the relevant levels of organisation.

Key challenges that emerge in Systems Medicine are:

- ▶ How to integrate experimental data from a wide range of technologies and sources?
- ▶ How to relate different modelling formalisms?
- ▶ How to integrate computational implementations?

These challenges can be addressed through multiscale modelling which requires the development of computational models that help to integrate data and knowledge from the clinics and basic science (*in vitro* and animal model experiments) and are applicable to individual patients, aiming at a mechanistic understanding of pathologies. The concomitant development of concepts, methods and tools that support the integration of data across organisational levels and that which can readily interface between different computational and mathematical approaches is also required.

Data analysis and mathematical modelling: A major hurdle for the development of quantitative and predictive models that span the gap between cell-level biochemical models and organism-level pharmacokinetic/pharmacodynamic (PK/PD) models is the technical difficulty associated with generating sufficiently comprehensive quantitative datasets for large numbers of system variables, across different levels of organisation. For the modeller, an exciting challenge is the development of models that can be used in clinical practice while accounting for the uncertainty in the data. Rapid advances in measurement technologies (e.g. next generation sequencing) and the apparent deluge of data could lead to an overemphasis on data management issues.

Three priority areas, towards which data analysis and modelling can contribute in Systems Medicine are:

1. Predicting drug/treatment responses for patients
2. Understanding disease risks
3. Integrating levels of functional and structural organisation

3 - Data generation

This is an abridged version of the output from Round Table 5: Generating Valuable Data for Simulation and Modelling Driving Systems Medicine at the 1st CASyM Stakeholder Conference, Lyon March 2013. The link to the full report can be found in Annex VII of this document.

Without the underlying data there can be no Systems Medicine. However the data required for Systems Medicine cannot be predefined as it is specific to each individual investigation. Instead of defining the type of data, we propose a Systems Medicine data generation methodology based on:

A systems method: This methodology aims to connect patient level outcomes and conclusions with an underlying mechanistic area of biology using systems modelling approaches. However, generating data on a large scale for all possible study areas is cost prohibitive.

A clinical relevant research question: In order to define realistic research hypothesis secondary use of existing data from Registries, clinical studies and Electronic Health Record sources could and should be used to define specific research questions and isolate populations of interest.

Suitable data generation: With a specific population selected, highly focused rich experiments could be carried by using data intensive methods of: Patient Reported Outcomes, Biopsies, Ex-vivo biology, Bio-sensing to capture the rich biological differences between these subjects in a way that was suitable for the modelling approaches.

Model based predictions: Modelling predictions about both the biological systems but how they translate into humans can then be deployed based on the rich data collected

Proper validation: The results of the modelling and analysis then need to be validated back in the healthcare setting by once again using existing data or running naturalistic experiments in clinical populations.

It is the hope that this type of methodology that comprises both secondary use of real world evidence data and focused rich biological data from small but targeted populations would enable research programmes that are innovative and insightful but also cost effective.

4 - Technological infrastructure

This is an abridged version of the CASyM Report *Technological and ethical requirements for sustainable knowledge management, integration and sharing in translational research and Systems Medicine*, Lyon, 25 June 2013. The link to the full report can be found in Annex VII of this document.

Systems Medicine must exploit knowledge from different disciplines, collaboratively advancing new insights into disease mechanisms, improving diagnostics and advancing therapeutic options through a process of collaborative understanding and effective communication. This requires a technological infrastructure that supports efficient integration of different levels of information and which can be tailored to the needs of the users. An important basis is the development of an agreement on data handling, storage and sharing and means to access the quality of knowledge utilized for the formulation of mathematical and computational models which can help to converge towards modular systems and data sources that reliably interact and form an interoperable, sustainable and usable system for clinical and non-clinical data, mathematical models and condensed knowledge. Key priorities are:

Establishing standards: The definition of parameters that have to be documented for each data point greatly facilitates assessment of the quality of data. Additionally, standardized documentation of mathematical models is required. The standardization process must be scalable and include clinical data, since this data is often incomplete and provides more qualitative information but is extremely valuable.

Improved knowledge gathering: A comprehensive collection of available disease models, both in experimental and mathematical terms, provides an important basis for Systems Medicine. To improve the process of knowledge acquisition, one should define the metadata that would complement this collection and define unambiguously the conditions of its acquisition. Furthermore the collaborative design of evidence grids to evaluate knowledge extracted from scientific literature greatly facilitates the process to provide a core data services and management and helps to provide a reliable archive as well as active support.

Unified solutions for data storage and exchange: The development towards a normalized solution for data storage and exchange with sufficient flexibility requires pluggable infrastructures and a knowledge based representation of literature, models, data and standards. It will greatly promote sharing of data and sustainability of public efforts. Structured, collaborative knowledge, data and model access will replace traditional literature and will greatly accelerate advances in medical science.

5 - Patient stratification for a more personalized medicine

A key medical problem is that an estimated 85 % of therapies fail in early clinical trials because of lack of efficacy or sufficient safety²³. In the US this corresponds to an annual cost of 350 billion dollars of ineffective drug prescriptions²⁴. There is therefore a clear need for stratification of patients for a variety of diseases. Better patient stratification is considered to be a tractable area that Systems Medicine could drive. With the large number of genes involved in complex diseases, advances in ‘-omics’ technologies can be key to improving patient stratification, from preclinical phase onwards. In addition, re-stratification strategies should also take environmental as well as lifestyle parameters into consideration.

Systems medical principles can be applied to personalise medication based on finding the specific combinations of disease associated genes per patient. Success in recent EC funded projects such as MultiMod (www.multimod-project.eu; see Annex V) show this is an important opportunity for Systems Medicine to make a significant impact on health outcomes for patients.

If patients can be stratified for personalized medicine this has important implications for future research: new drugs may be developed for patients that do not respond. It is also possible that gene variants or other genomic layers in the modules may be used to predict and prevent diseases. Step 1 and 2 may be performed on the huge ‘-omics’ resources available in the public domain, so that investigators can directly proceed to

stage 3. Therefore systematic large-scale analyses of public ‘-omics’ data from multiple diseases followed by clinical studies (steps 3-5) may be an important research priority to demonstrate the feasibility of Systems Medicine.

The following five steps towards patient stratification are seen as essential:

1. Interconnectivity: Modules of highly interconnected disease-associated genes are identified by messenger ribonucleic acid (mRNA) microarrays or ribonucleic acid (RNA) sequencing.
2. Validation: Those modules are validated by repeated analyses of independent materials. This includes analyses of mRNA, but also other genomic layers, for example by searching for enrichment of disease-associated single-nucleotide polymorphisms (SNPs) in the mRNA modules.
3. Disease function: Functional studies of modules to characterise the disease processes.
4. (non-)Responders: Analyses of modules in patients that do or do not respond to treatment.
5. Clinical study: Module genes or proteins are tried in prospective clinical studies to individualise medication. It is possible that such studies will include more than one sample from the same patients in order to stratify patients based on dynamic changes in disease processes.

6 - Working with Industry

This is an abridged version of the CASyM report *Europe-wide inventory of industry involved in applying Systems Medicine: Identifying areas of successful innovation and exploitation*, October 2013. The link to the full report can be found in Annex VII of this document.

The road map for Systems Medicine aims to speed up innovation in translational activities and to inspire scientists, management and investors with best practice in gaining rationally based cost-effective drug and technology development in their industry and in creating new industries based on a personalised, preventive, predictive and participatory Systems Medicine approach.

Within the broad category of ‘industry’ are a wide range of experiences and utilisations of Systems Medicine. From ‘big pharma’ companies attempting to yield more insights into the increasing volume of data they are producing, to technology-driven personal diagnostics operations who require modelling and

²³ Ledford: Translational research: 4 ways to fix the clinical trial. Nature. 2011 ([PDF](#))

²⁴ What happened to personalized medicine? Nature biotechnology 2012, Editorial ([PDF](#))

simulation tools, and SMEs positioned in niche markets who are often leading the way in their utilisation of Systems Medicine approaches. Interviews with representatives from across this spectrum indicated four major areas of industrial interest regarding Systems Medicine:

Elucidating mechanisms from disease data: Many companies in the field of modelling, technology development and drug development are already applying systems approaches. Systems Medicine is considered a requirement for a better understanding of disease mechanisms, portfolio optimization and for finding new technology, drug targets and patient subsets. Systems Medicine will accelerate the field towards personalised medicine.

Collaboration: Public-private partnerships (PPP) are highly appreciated and considered crucial, since they combine different areas and traditions in science and health care. PPP should always start and end with the need of the patient. And through open discussion, a clear focus on the gaps and technological challenges of the future (not of those of today) should be gained.

Proving the Concept: Lack of robust and widespread Proof of Concept restrains industry from making large-scale investments in Systems Medicine approaches (see Annex IV: Key Performance Indicators). Industry would benefit from an online proof of concept portfolio and a 'global standard' of quality guidelines for *in silico* approaches.

Getting access to data: Improved mechanisms for access to and use of patient data are needed for research purposes while ensuring the privacy of the patient. Computational models can only be built and used accurately when a sufficient amount of data of high quality is available and a data management infrastructure has been implemented. Focus should be made on specific disease subsets represented by homogenous and well-characterized patient subpopulations.

7 - Ethical and regulatory issues

This is an abridged version of the CASyM report *Technological and ethical requirements for sustainable knowledge management, integration and sharing in translational research and Systems Medicine*, June 2013 and roundtable discussions from the 1st stakeholder conference, Lyon 2013 on the Ethical and Regulatory Scenario of Systems Medicine and How to Improve the Involvement of Patients in Systems Medicine Studies. The link to the full report can be found in Annex VII of this document.

However, a major challenge in bringing P4 medicine to fruition is dealing with the impact of this approach on

society.

Here key ethical, social, legal, regulatory, and economic issues play a crucial role:

1. *Step towards P4:* Systems Medicine and in the systems biology and the digital revolution are together transforming healthcare to a proactive P4 medicine.
2. *Patient participation:* Citizens, both in health and in sickness, will be a major driver of the their own healthcare; to realise this, significant efforts in improving health literacy and education will be required to ensure advances benefit all rather than entrenching inequalities.
3. *Patient privacy:* A robust pan-European legal framework is required to protect the interests of individuals, their data and use thereof, as well as public education programmes to improve understanding of privacy issues.
4. *Health insurance:* With advances in the ability of medicine to predict illness and disease will come challenges to current paradigms of health insurance; a framework for health insurance and insurers will be required to ensure healthcare for all.

8 - Multidisciplinary training

This is an abridged version of the CASyM report *Should systems medical training be integrated for basic and clinical researchers?* September 2013. The link to the full report can be found in Annex VII of this document.

Systems Medicine training can become the unifying strand for medical education, creating a coherent link between the preclinical disciplines (chemistry, biochemistry, cellular and molecular biology, statistics and anatomy) whilst incorporating systems-specific learning in networks, statistics, data-handling and modelling. Major challenges include the training of current research MDs and clinical practitioners involved in the diagnosis and treatment of diseases who will require greater familiarity with genomics, data integration, bioinformatics, and '-omics' technologies in order to be able to incorporate them into their work. As such, Continuing Medical Education (CME) will be central, with educational information and training programmes for all career stages incorporating the latest modes of web-based learning.

Building on current international exemplar training initiatives (see below), a variety of modes of learning (Fig. 3) should accommodated facilitating i) modular, ii) integrated, iii) study-at-own-pace, and iv) cost-effective

training²⁵, to be combined with and improve on current training structures. These should be both, international and inclusive, applicable to a variety of healthcare workers from clinicians to paramedics and nurses as well as other professionals who will work across the spectrum of Systems Medicine-related roles.

International exemplar activities

- ▶ SysMIC - Comprehensive online course in the interdisciplinary skills. [\[more\]](#)
- ▶ BioHealth Computing Model – Interactive training initiative and comprehensive exchange programme between students, academia, hospitals and industry partners featuring conferences, workshops and advanced courses/research projects. [\[more\]](#)
- ▶ Systems Medicine training program of Georgetown University, USA – The only dual MD/MS program in Systems Medicine so far. [\[more\]](#)
- ▶ The CASyM Systems Medicine training tutorial, Ljubljana (2013). [\[more\]](#)

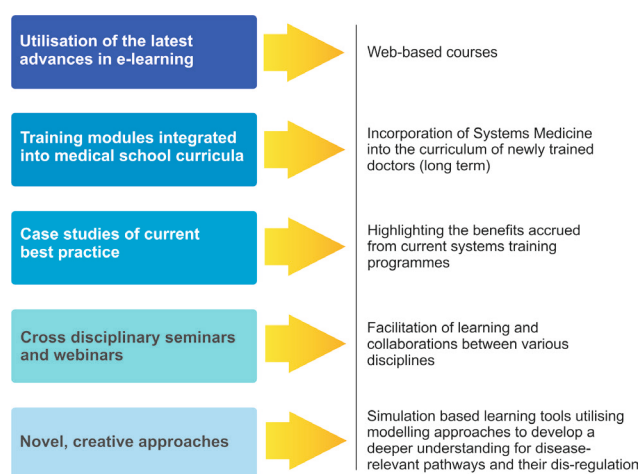


Figure 3: Key components of the Systems Medicine training concept.

9 - Stakeholder engagement: Community building, networking and disseminating the Systems Medicine concept

The construction of the Systems Medicine road map is based on a broad cross-disciplinary stakeholder consultation and community building process, centred on a series of focused conferences and workshops to collect expert views and opinions about essential topics for an implementation strategy for Systems Medicine. Each stakeholder group (see Figure 4) plays a vital role in the process of translating research into new predictive diagnostic tools and personalised, targeted therapies for patients. The consultation process was initiated with two major open stakeholder conferences and continues with a series of specialized workshops and training events (see Annex VI for underlying reports). This process has enabled core stakeholders to be identified and a dialogue initiated. A second level of stakeholder engagement into the road map process to review the findings of the initial stakeholder consultation is the institution of a Stakeholder Advisory Board (STAB). This extensive board consists of a range of experts covering our core stakeholder groups and CASyM Associate Partners whose rigorous input is vital to the formulation and direction of the implementation strategy for Systems Medicine.

The needs of clinicians and patients have been central to the road map's development, with clinical and patient organisation representatives incorporated into all aspects of deliberations. The challenge of giving a voice to the many stakeholders will be key to the success of this implementation strategy for Systems Medicine. It is anticipated that the formation of a new society or chapter of an existing society can continue to represent and engage with the wide range of stakeholders identified to date, promoting openness and inclusivity and developing and strengthening key networks.

Links to the EC, a core stakeholder straddling the spheres of funding and policy, are vital to ensure that the road map can effectively steer through a new way of thinking about medicine and medical research. The road map aims to build on the existing strong relationships between the EC and key actors within Systems Medicine.

²⁵ Voit EO et al. A feel for systems. Mol Syst Biol. 2012 ([PubMed](#))

Cooperation with other initiatives, patient interest groups as well as regulatory agencies and health care organizations are crucial for the successful implementation of Systems Medicine.

Since Systems Medicine is, as has been emphasised, an interdisciplinary concept. A key issue to achieve a successful Europe-wide implementation of this approach is the formation of interdisciplinary networks between:

- ▶ EU and national programmes related to the field
- ▶ Clinicians, disease-specific biology experts, systems biologists and bioinformaticians
- ▶ Regulators, patient and healthcare organizations, industry and funders

To date, under the aegis of CASyM, collaborative links have been developed with initiatives on the European Strategy Forum on Research Infrastructures (ESFRI) road map in the field of biomedical science, including Infrastructure for Systems Biology Europe (ISBE), Elixir and Biobanking and Biomolecular Resources Research Infrastructure (BBMRI). Central to this approach is the question of how existing/new infrastructures projects can engage with the relevant Systems Medicine communities to meet such needs necessary for a short term implementation process. These collaborations will ensure a coordinated approach to the development of infrastructure that will support the aims of the Systems Medicine road map, as well as promoting the added value that the systems approach can bring to other initiatives.

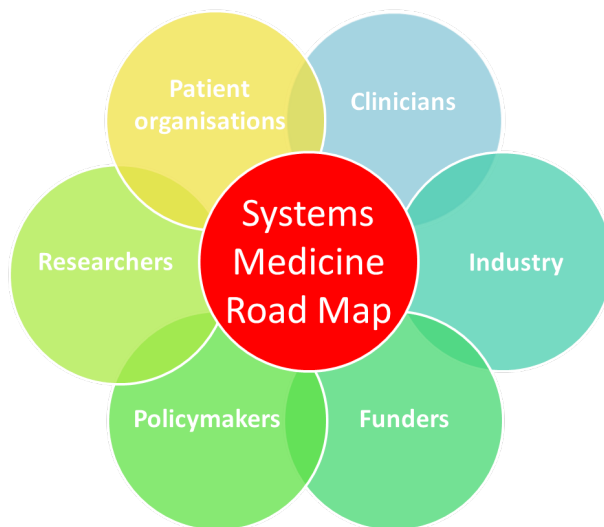


Figure 4: Stakeholders of the Systems Medicine roadmap.

10 - Integration of national efforts in Systems Medicine and within the EU

To ensure a sustainable emphasis on using the Systems Medicine approach to make a real, lasting benefit on health, understanding of disease, clinical trial design, funding policy and health economics, it is recommended that research be carried out on the establishment of a European Society of Systems Medicine, composed of representatives from across the stakeholder groups.

Key components for integrated efforts in Systems Medicine are the following:

- ▶ A willingness of public funders to collaborate on common pan-European initiatives to increase the impact of their funding programmes in Systems Medicine.
- ▶ Systematic development of pan-European research programmes that support a systems approach bridge between clinical, experimental and computational approaches (see also Annex III).
- ▶ Openness of private funders to engage on a European rather than a national or regional level.
- ▶ Support of pan-European initiatives in Systems Medicine by the EU that builds up networks of clinics and research centres and fosters the exchange between disciplines.
- ▶ Dedicated European support for integration and harmonisation on the scientific but also on the policy and ideally also the regulatory and legal level.
- ▶ The stable collaboration and interaction between major research centres pursuing systems approaches and research interested clinics cross-border in Europe.
- ▶ Creation of sustainable collaborative networks between computational, experimental and clinical groups in Europe.
- ▶ Establishment of an integrative and open community of researchers and clinicians to pursue systems approaches to health and disease, aiming at inclusivity rather than competition.
- ▶ Creation of a sustainable communication platform for researchers in Systems Medicine.

Recommendations

- ▶ Create a common forum of national and regional funding bodies to stimulate integration of national efforts.
- ▶ Funding of initiatives that harmonize and link activities in the different countries.

Core priority actions

What	How	Who	When	Progress
Investment in proof of concept	European funding for proof of concept projects that demonstrate technological and methodological feasibility, tangible clinical benefits, with clear potential, social and/or economic benefits of Systems Medicine.	Funders	Year 2	CASyM development of framework for characteristics of a good Systems Medicine project (Annex IV)
Paradigm shift through a community building effort	Cost analysis: Are the European health care systems financially 'ready' for the integration of systems medicine into clinical practice?	Researchers	Year 2	
	Conceptualisation of systems approach.	All stakeholders	Year 2	
	Development of a broad outreach programme to different audiences: public, patients, professional (clinicians) and politicians.	All stakeholders	Year 2	
Training programmes for scientists and clinicians	Development of European training agenda, with Systems Medicine educational workshops and mini symposia.	Researchers, clinicians, policymakers	Year 2	Process initiated through CASyM workshops
	Organisation of satellite training symposia at large clinical events.	Researchers, clinicians	Year 2	Process initiated through CASyM workshops
	University working groups to be established to develop and implement new Undergraduate (BA), Graduate (MSc), Doctoral and CME programmes listing also different available tools for different levels and different user groups.	Researchers, clinicians	Year 5	
	Sustained implementation of novel cross-disciplinary training programmes in Systems Medicine for the next generation of medical doctors and scientists.	Researchers, clinicians, policymakers, funders	Year 10	
Data access, data sharing and standardisation	European wide mapping of relevant ethical, regulatory and patient issues.	Researchers, clinicians, policymakers, patient organisations	Year 2	
	Development of new paradigms of recruitment of Systems Medicine based clinical trials.	Researchers, clinicians, industry	Year 2	
	Studies on patient and clinical data handling, with focus on standardisation, harmonization and sharing , defining global data sharing frameworks.	Researchers, clinicians	Year 2	
	Implementation of new guidelines at European level following on from patient data studies.	Policymakers	Year 10	

Table 1: Core priority actions for an implementation strategy of Systems Medicine in the short-, medium and long-term (see also Fig.1 and previous section).

Detailed priority actions

What	How	Who	When
Improving clinical trials	Shift towards a patient-oriented approach, integrating genetics and lifestyle dimensions.	Clinicians, researchers	Year 2
	Targeting of pathways instead of one drug, one disease.	Clinicians, researchers, industry	Year 2
	Considering co-morbidities and drug interactions.	Clinicians, researchers, industry	Year 2
	Adopting principles of adaptive trial design.	Clinicians, researchers, industry	Year 2
	Strategic identification of new disease taxonomies further favouring a pathway approach to clinical trials.	Clinicians, researchers, industry	Year 5
	Development of <i>in silico</i> clinical trial design.	Clinicians, researchers, industry	Year 10
	Access to high-quality, open access datasets to facilitate refinements in the identification of biomarkers, outcome measures and drug targets.	Policy-makers, clinicians, researchers, industry	Year 10
	Development of mature tools for integration of heterogeneous datasets with user-friendly interfaces facilitating usability by translational researchers.	Researchers, industry	Year 10
	Categorization of existing, deterministic and probabilistic modelling approaches.	Researchers	Year 10
Methodology and Technology – Modelling	Exploitation of existing data as a starting point for multiscale modelling, leading to the identification of gaps in data and in understanding of underlying mechanisms in order to improve the targeted generation of new data that can be exploited for quantitative models.	Researchers, clinicians	Year 2
	Define test scenarios and proof of concept studies.	Researchers, clinicians	Year 2
	Identify required standards and ontologies (e.g. a markup-language and ontology for individual-based models) for models and data repositories in Systems Medicine.	Researchers, clinicians	Year 2
	Development of concepts for dedicated modelling workflows for the integration of data and models.	Researchers, clinicians	Year 2
	Development of computational tools and algorithms for efficient multiscale simulations.	Researchers, clinicians	Year 5
	Development of mathematical formalism to analyse and compare multiscale models such as parameter estimation, sensitivity analysis, identifiability analysis, image analysis.	Researchers, clinicians	Year 5

Methodology and Technology – Modelling (continued)	Computational models that help to integrate data and knowledge from the clinics and basic science (<i>in vitro</i> and animal model experiments), applicable to individual patients, aiming at a mechanistic understanding of pathologies or support of therapy optimisation.	Researchers, clinicians	Year 5
	Development and roll out of strategic modelling workshops on multiscale modelling' s role in Systems Medicine.	Researchers, clinicians	Year 5
	Support the development of workflows for modelling, including computational tools that support data management, model construction and analysis.	Researchers, clinicians	Year 5
	Development of methods to integrate different physical phenomena, including of electrical, mechanical and chemical origin and methods to investigate the interplay between environment, cell behaviour and cell fate.	Researchers, clinicians	Year 5
	Creation of biomarker database.	Researchers, clinicians	Year 5
	Enhance the formation of small-scale networks focussed on specific clinical needs, possibly clustered in a larger integrated project (longer time scale).	Researchers, clinicians	Year 10
	Put in place a funding model for small groups of 2-3 partners (1-2 modelling postdocs, 1-2 experimental postdocs + consumables, travel between labs).	Researchers, clinicians	Year 10
	Targeted therapies for given phenotypes.	Researchers, clinicians	Year 10
Data generation	Studies on patient and clinical data handling, with focus on standardisation, harmonization and sharing.	Researchers, clinicians, policymakers	Year 2
	Efforts to collect and analyse data on: Non responder patients; healthy people; chronotherapy; side effects of drugs/genotypes; failed clinical trials; identification of gaps in data for Systems Medicine use.	Researchers, clinicians	Year 2
	Development of SOPs and quality standards for the systematic collection of quantitative data.	Researchers, clinicians	Year 5
	Implementation of new guidelines at European level following on from patient data studies.	Policymakers	Year 10
Technological infrastructure	Existing solutions for standards and solutions to be collected and utilized; review providing overview and evaluation of prior work.	Researchers, clinicians, policymakers	Year 2
	Develop inter-operable standards and software, together with relevant stakeholders and initiatives such as ISBE, ELIXIR and EATRIS.	Researchers, clinicians, policymakers	Year 2
	Development of incentives to adhere to newly develop standards to increase compliance.	Researchers, clinicians, policymakers, funders	Year 2
	Development of resources that enable the sharing of data sets and software.	Researchers, clinicians, policymakers	Year 5
Patient stratification	Development of a standardised and centralised '–omics' database describing modules in different diseases, as well as variations in such modules.	Researchers, clinicians	Year 2
	Development of compound database linking compounds to modules, and module variants (to individualise medication).	Researchers, clinicians	Year 2

Patient stratification (continued)	Development of modelling tools to individualise medicine for static and dynamic clinical use, including N=1 approaches.	Researchers, clinicians	Year 2
	Systematic analyses to re-exploit drugs that have not reached the clinic due to late clinical failure, in stratified subgroup populations based on systematic large-scale analyses of public '-omics' and physiology data from multiple diseases followed by clinical studies.	Researchers, clinicians, industry	Year 5
Working with industry	Development of Proof of Concept portfolio .	Researchers, clinicians, industry	Year 2
	Development of policy on open access to data from patients and healthy people.	Policymakers	Year 5
	Development of funding programmes specific for disruptive industrial innovation: national governments and EC facilitate disruptive innovation by means of specific funding schemes allowing for cooperation of scientists from academia, industry and clinics.	Funders, policymakers	Year 5
	Creation of international trade federation for SMEs: one to help non-experts discriminate between the various systems tools and applications, reducing the market's opacity and thus facilitating adoption.	Industry, policymakers, researchers, clinicians	Year 5
	The creation of a Proof of Concept platform based on the application of securitized financings to enable SMEs to generate IP. This requires the creation of a legal framework, an ecosystem of certified CROs and private and public investors.	Industry, policymakers, funders	Year 5
	Establishment of a method to evaluate <i>in silico</i> simulation results and associated quality standards for agencies (regulators and payers).	Industry, researchers, clinicians, policymakers, funders	Year 5
Ethical and regulatory considerations	European wide mapping of relevant ethical/regulatory/patient related issues to be accomplished.	Researchers, clinicians, policymakers, patient organisations	Year 2
	Research into the inequality and literacy of patients & operators correlated with highly technological systems approaches. Health Technology Assessment to be evaluated as a tool for accountability and sustainability matters.	Researchers, clinicians, policymakers, patient organisations	Year 2
	Development of a user-friendly ethical framework including provisions for accessibility to data by qualified researchers.	Researchers, clinicians, policymakers, patient organisations	Year 5
	Carry out lobbying actions to influence regulators who will build the appropriate legal framework to ensure that human genome information is freely available.	Researchers, clinicians, policymakers, patient organisations	Year 5
	Harmonize ethical regulations in order to build sustainable solutions to ethical, legal and social issues in the EU.	Researchers, clinicians, policymakers, patient organisations	Year 10

Training and outreach	Build an outreach programme to different audiences: public, patients, professional and politicians.	All stakeholders	Year 2
	Development of European training agenda, with Systems Medicine educational workshops and mini symposia in different countries including new member states.	All stakeholders	Year 2
	Clarify and establish responsibilities to educate stakeholders in Systems Medicine research.	All stakeholders	Year 2
	Develop education tool kit for all stakeholder groups.	All stakeholders	Year 2
	Align with medical societies and other stakeholders lobbying initiatives.	All stakeholders	Year 2
	Establishing links to the Innovative Medicines Initiative (IMI) educational programmes to avoid overlaps and close gaps.	All stakeholders	Year 2
	Establishing links to European Medicines Research Training Network and set up a working group with different training initiatives.	All stakeholders	Year 2
	Emphasis on education for patients to understand principles of Systems Medicine and P4 Medicine so they can participate (responsibly) in their process along with physicians of the healthcare community, with a tool kit adaptable to diverse populations & cultures.	All stakeholders	Year 2
	Research on range of new positions that will need to be created to embed systems practices in clinic and hospital environments; development of relevant training courses.	All stakeholders	Year 5
	University working groups to be established to develop and implement new Undergraduate (BA), Graduate (MSc), Doctoral and CME programmes listing also different available tools for different levels and different user groups.	Researchers, clinicians	Year 5
Stakeholder engagement: Networking and disseminating the Systems Medicine concept	Sustained implementation of novel cross-disciplinary training programmes in Systems Medicine for the next generation of medical doctors and scientists.	Researchers, clinicians, policymakers, funders	Year 10
	Research viability and appetite for a European Association of Systems Medicine; establish Association if demand adequate.	All stakeholder	Year 2
	Establish links and synergies with other related initiatives, including projects on the ESFRI road map.	Researchers, clinicians, policymakers	Year 2
Systems Medicine impact factors	Raise awareness among politicians about economic opportunities that open availability of personal genome information.	Researchers, clinicians, policymakers	Year 2
	Establishment of comparative pilot case studies (classical vs. Systems Medicine).	Researchers, clinicians, funders	Year 2
	Directed assessment of current Systems Medicine applications in analysis studies (state of the art).	Researchers, clinicians, funders	Year 2
	Establishment and use of retrospective cohorts to analyse Systems Medicine efficiency.	Researchers, clinicians, industry	Year 2

Systems Medicine impact factors (continued)	Development of self-assessment methods for hospitals and subsequent mapping of clinical Systems Medicine application in Europe.	Clinicians, policymakers	Year 2
	Establishment of integrated patient assessment centres for best-practice application of and data generation from clinical Systems Medicine approaches.	All stakeholders	Year 5
	Establishment of new and support of existing prospective patient cohorts.	Researchers, clinicians, patient organisations	Year 5
	Implementation of guidelines for monitoring of Systems Medicine implementation in health care systems and education.	Researchers, clinicians, policymakers	Year 10
	Development of rules for evaluation of Systems Medicine-related education and health organizations/institutions.	Researchers, clinicians, policymakers	Year 10
	Labelling of health care organizations/institutions actively pursuing Systems Medicine approaches.	Researchers, clinicians, policymakers	Year 10

Table 2: Detailed priority actions for an implementation strategy of Systems Medicine in the short-, medium and long-term.

Annexes

Annex I: CASyM and Systems Medicine

The Coordinating Action Systems Medicine (CASyM) is a multidisciplinary European consortium that is charged with developing an implementation strategy (road map) for Systems Medicine. This CASyM road map is driven by clinical needs: it aims to identify areas where a systems approach will have an impact on addressing clinical questions and will solve clinical problems. CASyM is supported for a period of four years until October 2016 by the European Union through the 7th Framework Programme (FP7), Theme Health.

CASyM is not a standalone project; it wants to integrate and complement the numerous Systems Medicine initiatives across Europe. CASyM is about medicine, and a significant part of this is clinical medicine, from clinical trials through public health and data handling, to application of Systems Medicine and medical economics. However, Systems Medicine also needs to prove that it not only leads to a health benefit, but also to an economic and social benefit. Cost savings have to be demonstrated by specific examples, since Systems Medicine needs to be cost effective in order to be successful. Still, due to the inherent complexity of a patient, cost might also rise initially, when Systems Medicine approaches will be applied in the clinical setting. Above all CASyM wants to deliver Systems Medicine as a new concept, a way of thinking and an attitude that goes beyond traditional omics/informatics, experimental medicine and clinical trials. Systems Medicine is the most promising way that P4 Medicine can be delivered.

A major impact indicator as that if CASyM continues as the Association of European Systems Medicine because there is a perceived need for it. Acceptance and sustainability will depend on the credibility across multiple stakeholders (industry, European Commission, clinicians, public, policy makers and regulators and so

on). CASyM wants to become a unified voice speaking for the stakeholders in Systems Medicine and articulating their vision and goals. Close links to funding cycles and approval of funding is likely to be both necessary to “hardwire” Systems Medicine in Europe but also to demonstrate its credibility. Success stories are vital in achieving this.

Stakeholders/events in CASyM

To make the clinical needs central to this road map, the clinical voice was heard in all aspects of deliberations and work during the development of this road map. Any scientific, systems biology approaches must be heard through clinical voices, so as to maximize the chances of credibility. Relevant stakeholders were asked to select a range “of most crucial” topics, but there were also discussions on visions or on how to decide on a “generic Systems Medicine road map” as wide as visionary. Discussions on legal and ethical questions of genome interpretation, patients’ privacy rights and the necessity to use the data for P4 medicine were held in parallel.

Participative engagement means that the end of CASyM will see a valid output that may be quite different from anything hitherto envisaged: CASyM wants to be sufficiently flexible to be inclusive (that is, not a threat to anyone else) and yet distinctive (presenting a new coherent vision). Patient organizations, representing patient’s needs are considered key stakeholders when it comes to a general acceptance of the Systems Medicine approach. Particularly within P4 Medicine, the patient plays an active role and needs to be truly convinced that this concept is beneficial. Patients need to be included to perform longitudinal studies. Therefore, patients (their interest groups) need to be invited to take part at the road mapping process and proper protocols need to be provided, explaining challenges, possibilities, benefits and actual clinical practice. Links to the EC are important so that CASyM can effectively steer through a new way of thinking

about medicine and medical research. Therefore CASyM aims to establish close interactions with the European Commission.

CASyM organized two major stakeholder conferences to obtain expert input for drafting this Systems Medicine road map. This road map was drafted from the conclusions of these stakeholder meetings as well as a series of accompanying focussed workshops (see below). The first stakeholder conference was a large event aimed at covering all relevant stakeholders and addressed multiple topics relevant for an implementation strategy for Systems Medicine. CASyM organized this stakeholder meeting, in Lyon on March 25-26, as a satellite event of the Biovision International Forum of Life Sciences. The second event focused on clinical thematics and was specifically organized for the clinical community. During the subsequent second CASyM stakeholder conference on May, in St Andrews, United Kingdom, a smaller series of four round tables was organized to specifically investigate examples of real medical problems and to determine what areas are tractable using Systems Medicine approaches. The invited participants were selected based on their expertise in the four respective focus areas and their direct links to the clinic or involvement in patient organizations.

In addition to the initial two stakeholder conferences, CASyM organized a series of focussed workshops and tutorials concentrating on the following specific topics:

Strategic modelling workshop, June 2013, Heidelberg, Germany: The Role of Multiscale Modelling in Systems Medicine. A number of clinically relevant questions formed the background and motivation for this meeting, such as the origins of variability in the response of patients to drugs, the mechanisms that link the biochemistry of molecular interactions with biophysical processes and their micro-environment or the ways in which clinical and patient data can be analysed in combination with basic research data from pre-clinical experimental models. See also the accompanying publication by Wolkenhauer O. et al. 2014 [[more](#)].

Systems Medicine training tutorial, June 2013, Ljubljana, Slovenia: Systems Medicine of Multifactorial Disorders - workshop & tutorial and 8th CFGBC symposium. This CASyM event was a pilot in the sense of being a

“Systems Biology and Systems Medicine training proof of concept” upon which additional and similar events will build on as a part of a future education and training portfolio. The workshop and tutorial were accredited with 5 ECTS (European Credit Transfer System), 20 CME (Continuous Medical Education) and 20 SILM (Professional Education for Laboratory Medicine) points, which may well have been awarded for the first time in Europe for Systems Medicine in particular.

Technological and ethical focused workshop, June 2013, Lyon, France: The Road from Reactive to Proactive Medicine. This workshop focused on the technological and infrastructure requirements for sustainable knowledge management as well as on ethical, legal and social issues in personal data protection and sharing

CASyM/ICSB2013 training workshop, September 2013, Copenhagen, Denmark: Should systems medical training be integrated for basic and clinical researchers? Complementary to the training tutorial in Ljubljana this workshop was part of the CASyM educational activities to develop novel concepts to train the next generation of medical doctors and scientists in multimodal Systems Medicine approaches and took place in the context of the ICSB2013. With regard to the development of novel education and training concepts for the next generation of scientists and medical doctors there was a consensus amongst the meeting participants that Systems Medicine needs to be implemented as a discipline over the next two decades in a multi-layered fashion.

Cancer workshop, January 2014, Genoa, Italy: Clinical needs in oncology and cardiovascular diseases as drivers for a Systems Medicine approach. This workshop specifically focused on the needs and opportunities for a systems approach in two major pathologies.

Detailed reports to all events and frequently updated information can be found on the CASyM website [[more](#)].

ANNEX II: Application examples for Systems Medicine

These application examples are the result of clinically focused roundtables featuring experts from our core stakeholder groups utilising the Road Map Methodology (Annex VI). Further information can be found in the conference and workshop reports on the CASyM website [\[more\]](#).

Systems Medicine in drug development

State of the art: Present practices in drug development involve high levels of quantitation, but with limited systems thinking. The hypotheses that are being developed, and the tools that are used at the moment are reductionist, since the problems they are dealing with are very complex. But does this reductionist view still correlate with what actually happens in vivo? Diseases are complex, and there is a need to consider this complexity during drug development.

Most pharmaceutical companies acknowledge a need for systems thinking. Pharma however generally does not use mathematical modelling on its own to predict clinical outcomes. However, the panel pointed out one company that specializes in mathematical modelling of clinical outcomes: Immunetrics (Pittsburgh). One of the problems is that the structure of the pharmaceutical industry hampers the uptake of systems thinking while the pharma pipeline workflow is also very resistant to change.

Needs: Drug attrition due to lack of efficacy is still very common, however the percentage of attrition of drugs that is down to pharmacokinetic properties is reduced. On the other hand, it was shown that attrition during phase II and phase III of clinical trials is very high. The cost-effectiveness of drug development is therefore very low, with high levels of risk compared to the benefits of the current process. There are also high safety hurdles to overcome. Another issue is that when new diseases are pursued, there is less information for these groups of patients, with again very high cost and risk implications.

An improvement of the processes during phase II and III would therefore have the biggest impact on drug development. There is, in other words, a clear need to redesign the process of drug development. This should not just result in new compounds, but also in new

interventions (maybe using already available compounds), and a better stratification of patients.

There is also a need for more mechanistic data on diseases. Academics are not involved sufficiently closely in the drug development process. They could provide some more basic mechanistic data, which could assist in the processes of target validation. They could also help with data on tumor/disease heterogeneity. This data could teach us better if we are targeting the right person with the right drugs.

There is a need to assess which processes need to be brought together and how to use the data that are gained from bringing them together. There also need to be clarity on what areas healthcare is willing to pay for.

Opportunities for Systems Medicine: There are several opportunities for Systems Medicine to increase the probability of success during drug development.

In the short term, considering dose, regimen and timing of compounds could benefit from systems biology approaches. It is really important to correctly consider dose, target, etc. Oxaloplatin for example, was initially considered too toxic in phase I, but rather than shelving the drug after this initial phase, research on it continued and oxaloplatin is now a treatment for colorectal cancer.

Chronobiology, for instance, is a relatively new field that with the help of systems biology approaches changes our way of thinking on the timing of medication. Systems biology tools can be used to optimize regimen, considering multiple inputs, such as the kinetics of compounds.

In the medium term, Systems Medicine could help at the level of the patient population: systems biology techniques could help at the level of prognosis and prediction and could help to better stratify patients.

There is the opportunity to reposition already existing drugs, which some pharmaceutical companies are already in the process of doing. Key questions are: Are we using enough markers? Are the markers we use good enough? Are we targeting the right patient with the right drugs? Systems biology approaches however could help to get a better stratification. One approach is to take a population and assess it, then cluster the patients to understand the heterogeneity. There is a

need for using existing drugs to hit a target to test hypotheses. There is a need to access enriched populations for this approach. Recruitment for screening becomes more and more an effort, with a tenfold increase in the number of patients required, and at the same time the constraints of the desired cohorts become more stringent, resulting in a discount of the vast majority of the population.

CASyM could be very useful to “bringing interdisciplinary groups together”, for example pharma, clinicians, computational biologists and researchers working in a particular disease area, such as a specific area of oncology. These interdisciplinary groups should determine what the *current state of dynamic models is and what a tractable project is to push forward with systems thinking*. Such groups could “join the dots” and potentially allow fast progress, if a suitable area and the appropriate modelling tools are being identified.

Strategy / implementation: Two key actions need to happen to implement Systems Medicine in drug development. First of all, there is a need to perform a *systematic review of Systems Medicine dynamic models* in specific disease areas. It is important that this happens in interdisciplinary groups, in the right disease areas and that a correct group of participants is identified. A threat is that one could get lost in details of the many dynamic models that could be available. It is also important to decide on the acceptance threshold to know when a systems dynamic model is ‘working’.

The second key action is to develop exemplar systems dynamic models that are both descriptive and predictive. These models should be open to new inputs. They should be able to encompass experimental and clinical heterogeneity, using data from other or different sources. These exemplar models will showcase the Systems Medicine approach, with the concomitant result of helping with the uptake of Systems Medicine thinking and processes in the pharmaceutical industry.

These actions require a disease prioritization process. Respiratory diseases, oncology, infectious diseases and vaccine development are considered tractable and amenable areas for Systems Medicine approaches and thinking.

Summary

Drug development

State of the art

- ▶ Current mainstream reductionist approach to drug development has limitations
- ▶ High cost of present model
- ▶ High levels of quantitation, but with limited systems thinking
- ▶ Diseases are complex, and there is a need to consider this complexity during drug development
- ▶ Pharma pipeline workflow is also very resistant to change
- ▶ However, recent developments in systems pharmacology show growth in interest of systems approach

Needs

- ▶ Drug attrition due to lack of efficacy is still very common, however the percentage of attrition of drugs that is down to pharmacokinetic properties is reduced
- ▶ Attrition during phase II and phase III of clinical trials is highest
- ▶ Cost-effectiveness of drug development is very low, with high levels of risk compared to the benefits of the current process.
- ▶ New compounds, new interventions (maybe using already available compounds), and a better stratification of patients.
- ▶ More mechanistic data on diseases; greater integration of academic researchers into the drug development process.

Short term

- ▶ Potential benefits of systems biology approaches to dose, regimen and timing of compounds.
Oxaloplatin for example, was initially considered too toxic in phase I, but rather than shelving the drug after this initial phase, research on it continued and oxaloplatin is now a treatment for colorectal cancer.
- ▶ Chronobiology biological improvements: Systems biology tools can be used to optimize regimen, considering multiple inputs, such as the kinetics of compounds. The kinetics of antibodies are more predictable, and that antibodies can be dosed higher

Medium term

- ▶ Repositioning of existing drugs
- ▶ Improved patient stratification
- ▶ Interdisciplinary systems approach can bring the various stakeholders in drug development together

Strategy / implementation

- ▶ Phase 1: systematic review of Systems Medicine dynamic models in specific disease areas
- ▶ Phase 2: development of exemplar systems dynamic models that are both descriptive and predictive. These models should be open to new inputs, able to encompass experimental and clinical heterogeneity, using data from other or different sources and will showcase the Systems Medicine approach

Disease example: Non-cancer lung-disease

State of the art: As there is already some work in progress in the asthma field, this round table discussion did not focus on this disease, but rather focused on chronic obstructive pulmonary disease (COPD). Systems Medicine has not answered any of the big questions in the COPD field. Biobridge (FP6) is the only completed project, and though it delivered a workable portal the question remains whether the field has gone beyond what was being done and discussed in 2006.

What is already accepted in the field is that there is a need for integration of the ever-increasing variety and quantity of biological, clinical, epidemiological, environmental, functional, genetic, genomic, imaging, pathological and physiological data through systems approaches. This integration of greater quantity and quality of data will form the cornerstone for the personalized treatment (P4 medicine) of individuals.

Needs: There is a need for the development of an easy to access decision-support system for clinicians. This toolbox would consist of a panel of indicators for disease control. It could help in the monitoring of complex, heterogeneous diseases as COPD by both the patients and their physicians. This would be P4 medicine in practice.

There is a great degree of heterogeneity at the anatomical and pathological level. By using the current way of setting up clinical trials, one loses this heterogeneity. The current classification of patients therefore forms a problem. The COPD field is still

designing hypothesis-driven studies. This approach is biased and fails to integrate patients. The use of respiratory-driven criteria is not integrating the multi-morbidity aspect of this disease. There can for instance be a cardiac component to the disease. 25-30% of patients also have cognitive issues, and these are not involved in trials. Therefore these groups can be missed out. There is a very clear need for looking at all these co-morbidities at the same level. A big problem is that we lack the data of these co-morbidities. It was pointed out that this was one of the problems of the EU ECLIPSE project. There is currently no systematic approach to this lack of data. There is also a need for standardization of specimen and data collection.

Opportunities for Systems Medicine: At this point, there are only isolated impacts in the field. If COPD as a whole will be used as a more holistic starting point, one would come to a new taxonomy. The panel therefore saw the necessary redefinition of (multidimensional) COPD taxonomy as THE challenge for a Systems Medicine modelling exercise.

Systems biology approaches can help to incorporate the heterogeneity of the disease in clinical trials. Other criteria than the current respiratory-driven ones can be used to stratify patients. If this is done systematically, it can improve on the current sole human judgment.

For specific interventions, on the other hand, new cohorts will need to be recruited. From the first CASyM stakeholder conference in Lyon, it was clear that there is a need for a new paradigm of recruitment of Systems Medicine based clinical trials. However, it was also pointed out here that changing the established procedures in clinical trials will be very difficult and it was estimated to take about 20 years. It would be easier to change the eligibility criteria rather than changing the established methodology.

Implementation: In the short-term, there is a need for definition of the model requirements to develop this new taxonomy, and selection of the appropriate tools. This should also include standardization and harmonization of data.

Two modelling approaches were compared. First of all a top-down approach, where the distribution and co-existence of chronic disease is studied through a hypothesis-driven approach: based on existing disease

ontologies (i.e. classical diagnostic criteria and phenotypes). On the other hand, there is a bottom-up approach, via the modelling of novel, more complex phenotypes, including co-morbidities, risk factors, drug response and socio-economic determinants. This approach would use hypothesis free statistical models and data from patients. It was pointed out that gathering information of unusual cases can prompt new phenotypes. Therefore it is important that if Systems Medicine is based on statistical approaches that outliers are considered too. This hypothesis free approach would be co-morbidity focused, by applying systems biology approaches to overlap comorbidities. The use of a bottom up approach was therefore suggested having the greater utility. There was a reference to the Escher picture *Sky & Water I* (below): there is a big complexity in the middle between birds and fishes that we do not know about at this point. Similar to this, there is a big complexity at the level of the patient.

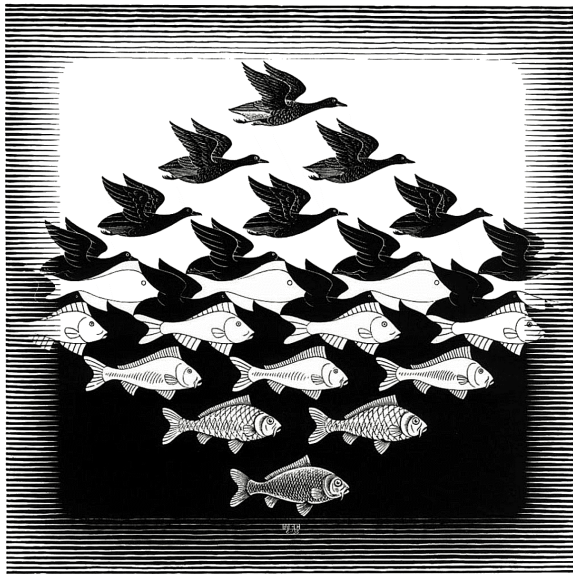


Figure 5: M. C. Escher, *Sky & Water I*, woodcut, 1938

One of the big problems is the incompleteness of data, and the lack of access to data. This first phase of generating a new taxonomy, should therefore also include efforts to enhance the data availability, standardization and harmonisation. Bioinformatics can help to close the gaps in data, and the development of standard operation procedures for data and specimen collection is necessary too.

Another issue is that the current healthcare and healthcare IT systems are not designed for this Systems Medicine approach. There is a clear need for a system

to move data between different users. One thing that was suggested is that the patient should remain the owner of the data, and not the GP or specialist. There must be confidence in the data that are collected; it can often be misleading and subjective. Patients for instance lie about smoking, for different personal reasons. There are also all kinds of other environmental factors that the patient would not report on, because he/she is unaware of them. All of these issues could lead to problematic conclusions. There should therefore be a stepwise approach, with adequate educational support that improves the patient-doctor relationship.

In addition, there are big socio-economic issues for the recruitment of patients to cohorts that need to be addressed. A GP has a very limited time with a patient. There is also a big gap that needs to be bridged between the GP and those designing the clinical trials. Again, it is the GP's that will have best access to the actual data. Explaining the importance of trials to different socio-economic groups can be challenging. GP's also don't see research as part of their job. They see it as a separate business.

The first, short-term phase should already result in a Systems Medicine clinical platform that provides a more dynamic and deeper understanding of more underlying mechanisms of COPD.

Subsequently, in the *mid-term*, there is a need for a thorough validation phase, both of the model requirements and of the standard operation procedures.

Validation of these actionable new-taxonomy driven interventions would happen through the use of solid clinical benchmarks, such as 'severity, activity and impact':

1. *Severity (degree of functional reserve)*: FEV1; IC/TLC; Arterial Oxygenation; exercise capacity
2. *Activity (doesn't go in parallel with severity)*: rate of change of FEV1, continued smoking, frequency of exacerbations; persistence of systemic inflammation (circulating leukocytes; C-reactive protein; IL-6; fibrinogen and selected biomarkers (!);
3. *Impact (degree of perception)*: COPD Assessment Test; mMRC

The use of 'severity, activity and impact' in the Netherlands makes it not necessary to see the patients very regularly, as the patient has some degree of self-management.

On the longer term (5 years) this Systems Medicine approach would lead to a modelling platform that can provide recommendations for clinical decision-making. These would be data driven models, based on validated 'outcome measurement' parameters (severity, activity and impact). Computational recommendations still will have to be complemented with clinical instincts, as a wrong input could have disastrous impact. Based on this modelling approach, clinicians would be able to use actionable, innovative, validated therapeutic strategies.

Summary

Non-cancer lung-disease, with focus on chronic obstructive pulmonary disease (COPD)

State of the art

- ▶ Lack of integration of the ever-increasing variety and quantity of biological, clinical, epidemiological, environmental, functional, genetic, genomic, imaging, pathological and physiological data
- ▶ COPD is increasingly recognized as a multicomponent heterogeneous disease with a lot of comorbidities. The heterogeneity in COPD lies at the pulmonary and extra-pulmonary level and beyond.
- ▶ At the moment, the field is trying to use reductionist methods, ignoring the heterogeneity

Needs

- ▶ Need for an easy to access decision-support system for clinicians; toolbox consisting of a panel of indicators for disease control
- ▶ Rigidity of current patient classification ignores great degree of heterogeneity at the anatomical and pathological level, ignores co-morbidities – new taxonomy required
- ▶ Standardization of specimen and data collection.
- ▶ Opportunities for Systems Medicine
- ▶ Systems approach can make sense of heterogeneity patients, giving clinician a holistic view of co-morbidities that is currently absent
- ▶ Focus on tractable problems

Short term

- ▶ Development of Systems Medicine clinical platform that provides a more dynamic and deeper understanding of more underlying mechanisms of COPD
- ▶ Model requirements for new taxonomy: bottom-up approach, via the modelling of novel, more complex phenotypes, including co-morbidities, risk factors, drug response and socio-economic determinants
- ▶ Central role of the General Practitioner
- ▶ Mix of new and old cohorts to be engaged, utilising historical data, where available
- ▶ Standardization and harmonization of data utilising advances in bioinformatics.
- ▶ Improvement of healthcare IT systems to accommodate systems approach

Medium term

- ▶ Validation phase, both of the model requirements and of the standard operation procedures using of solid clinical benchmarks, e.g. 'severity, activity and impact
- ▶ Investment in training and education for clinicians and patients

Long term

- ▶ Development of modelling platform that can provide recommendations for clinical decision-making.
- ▶ Based on this modelling approach, clinicians would be able to use actionable, innovative, validated therapeutic strategies.

Disease focus: Infectious diseases

State of the art: Infectious diseases are responsible for more than 13 million deaths a year, and have a particularly high impact in developing countries, where they account for one in two deaths. These diseases are the world's biggest killer of children and young adults, accounting for half of all premature deaths. They are a significant burden on global economies and public health.

Six diseases in particular are particularly prevalent, causing 90% of infectious deaths:

1. *Pneumonia*: Kills more children than any other infectious disease, with 10,000-40,000 in the average influenza season in the US alone;
2. *Tuberculosis*: One of the leading causes of death by infection worldwide. There are currently efficient treatments in use but they are prolonged treatments and require a combination of different drugs. Challenges therefore include the shortening of treatment and defining the best drug combinations, based on data on bacterial multiplication and the occurrence of resistance;
3. *Diarrhoeal diseases*: Claim two million lives a year among children under five (Including cholera, dysentery, typhoid, rotavirus)
4. *Malaria*: Globally, an estimated 3.3 billion people were at risk of malaria in 2011, with populations living in sub-Saharan Africa having the highest risk of malaria infection. Approximately half of the countries with an ongoing malaria transmission problem are on track to meet the World Health Assembly target to achieve a 75% reduction in malaria case incidence rates by 2015, compared to levels in 2000. In 2010, the estimated number of malaria deaths was 660,000;
5. *Measles*: One of the most contagious diseases, and is responsible for approximately 900,000 deaths a year;
6. *HIV/AIDS*: There are currently 33 million people living with HIV/AIDS globally. Challenges here include dealing with the new expectations of patients to make living daily life with the disease acceptable: mastering virus transmission; better focus on prevention, adapted to individual behaviours and pre-contamination treatment.

Further important areas include Sepsis, 15-19 million cases of which occur worldwide each year. The annual

cost of hospital care for patients with severe sepsis in the USA has been estimated at \$16.7 billion. With its complex interplay between regulation systems, leading to explosive behaviours, sepsis could be well suited to a systems approach.

Early intervention and prevention are key issues in this field; a systems approach would also need to deliver practical outcomes applicable to third world as well as first world needs. There is scope for optimization of currently employed treatments, while research on the interaction between chronic and infectious disease is underdeveloped. Deciphering the potential of zoonoses, which represent 60% of the emerging diseases at the global scale is also a significant challenge at present in the field²⁶.

The field includes a wide variety of stakeholders, from patients and clinicians to researchers, the pharmaceutical and medical device industry, regulators, health care and research funders. The challenge of bringing these disparate groups together could be addressed using a multidisciplinary approach and could reap significant rewards. In terms of drug development and discovery, it was noted that infectious diseases are often not treated with novel drugs, in contrast, for example, to cancer. The use of Systems Medicine in cancer therapy is quite progressed, the question is why is this not true in fields as infection?

Needs: The field of infectious disease is broad and multi-faceted and currently faces many challenges. From the need for rapid diagnosis and treatment to the standardisation of clinical data and the development of new drugs, there is an array of issues that require attention.

There is a diagnostic challenge of particular relevance to infectious diseases as well-established phenotypes are not available due to the lack of clinical data. This makes an early, accurate decision critical and difficult. Multiple treatments (polypharmacy) for multi-morbidities are currently monitored with only a few physical parameters (e.g. blood pressure/heart rate) and there is no good measure for a successful therapy available.

A rapid and deep prognosis/diagnosis within 24 hours is often required for infectious diseases. Key is to properly capture the clinical phenotype. Currently, there is no standardized sepsis phenotype for instance—clinical results are often recorded on the ward with varied quality. To improve diagnostic measures at a molecular level, the potential of rapid bedside

²⁶ Jones KE, et al. 2008. Global trends in emerging infectious diseases. *Nature* 451:990–994

sequencers/molecular diagnostic tools should also be explored which can guide therapy and provide a diagnosis within a very short timeframe. This is an area of on-going technological research. The use of mass spectrometry for instance is currently being developed as a technique for use at the bedside in some hospitals. However, this is depending on hospital policy. Further research also needs to be carried out on automated liquid culturing, which can provide faster, less labour-intensive and less expensive results than traditional methods of mycobacterial detection.

A related issue highlighted at the round table was the importance of clinical information and improved patient phenotyping. The current lack of standardised, high quality and exchangeable data is a major obstacle to both the effective treatment of infectious disease and the implementation of a systems approach. To meet the needs of rapid diagnostics, large-scale databases with real time facilities should also be available at the bedside. There are at present many gaps in different databases and data input is of variable quality; it would be beneficial, therefore, to implement a European infrastructure for data collection, storage, exchange and visualisation which could manage this complex task and give access to high quality bioinformatics and harmonised e-health records to clinicians and researchers.

Tackling antibiotic resistance is one of the biggest single issues faced in the field of infectious disease, causing the redundancy of previously effective drugs. The round table agreed that this issue is well suited to a systems-based approach. This topic is of great importance and a multidisciplinary approach involving clinicians, chemists and industry could be successful within ten years. As a part of this effort, it was suggested that a small molecular library should be developed and that new clinical trials would be needed. Human safety in testing represents an issue and properly working humanized animal models, as alternative systems to standard animal/in vitro models, are needed. Modelling of whole organs and organisms as considered still too difficult to be put in practice and will need years of further and continuous development. Genomic resistance profiles can display important key features for a potential therapy, where many patients might be potential carriers for multi-resistant strains. A proof of concept for genomic resistance profiles is already available through the work of the Wellcome Trust Sanger Institute in the UK.

At present, the translation of research into policy is a slow and difficult process, and can hinder efforts to tackle potential disease threats. In order to react quickly and efficiently to such pandemic outbreaks, a

well-established and specific research rapid alert system is needed.

Other issues briefly discussed include the necessity for further research on the links between chronic diseases and infectious agents; the importance of focusing on the elderly as a group who are highly prone to infectious diseases; and the difficulty of employing a systems approach across the board with the challenging variety of infectious diseases that exist, with timeframes for diagnosis and therapy which can range from minutes in the case of septic shock to years, as in HIV infection.

Opportunities for Systems Medicine: The round table panel identified the issue of tackling anti-infective resistance as a subject of particularly high importance in the field that would benefit from a Systems Medicine approach. It was suggested this could be best tackled at a European level.

As evidenced by the current state of the art in this field, there is a global market for tackling anti-infective resistance as well as good public understanding of the issues. The opportunity to have a significant impact on lowering mortality could make this a high profile option for a systems approach. However, as detailed above, substantial challenges in the areas of data management and standardisation are potential obstacles, as are health system inertia and the complexity of the issue. In addition, there are a range of important issues within the field of infection that could benefit from systems approaches.

The use of omics data for diagnosis could provide a high impact at the short term. Examples here are the use of mass spectrometry signatures and genomics to distinguish between species. Knowledge on species and the development of drug resistance should be kept in accessible databases. Computational systems chemistry could be employed to assist in antibiotic discovery whilst a systems approach could have a high impact in the short term in the early diagnosis of nosocomial infections.

Further short term actions could include the creation of standardised electronic health records for patient data, thus improving the quality of datasets available to researchers. Attention should also be given to clinical endpoints; for instance, it was questioned how we can measure 'cure' in TB, when relapse and reinfection remains an issue.

In the medium term, Systems Medicine could help at the level of antibiotic resistance through a series of small and focused multidisciplinary research initiatives incorporating clinicians, researchers and industry.

Better patient phenotyping tools should be developed, allowing diagnosis and response prior to the disease, rather than the current reactive response to outbreaks. There is thus a need for a more 'real time' follow-up of patients, which would ring alarm bells earlier. These data could also be used for post-analysis, for the improvement of developed algorithms.

Longer term aims include the development of new antibiotics, requiring new bacterial focused compound libraries. Further research on the links between infection and chronic health could have a significant impact and this will also require improvements to patient phenotyping. The implementation of early warning systems for pandemic outbreaks utilising the multidisciplinary expertise of Systems Medicine is also a key long term goal, incorporating front line health practitioners as well as scientists and researchers.

Implementation: As stated above, this round table panel identified tackling anti-infective resistance as a subject of high importance in the infection field that would benefit from a Systems Medicine approach. A series of actions are required to enable Systems Medicine to deliver important results for this challenge. Primarily, the creation of a European infrastructure for data collection, storage and exchange would provide access to centralised high quality bioinformatics databases, as well providing guidelines to support other shared clinical databases. The infrastructure would also function to bring together clinicians and researchers working on complementary issues. To ensure the infrastructure is pan-European, it is vital that policies be developed at a European level to facilitate exchange of data between countries. The collection of longitudinal patient observations would have to be central to this effort, enabling the monitoring of changes to the microbiome over the course of patients' lives.

A key output that would have significant impact would be the development of a bedside rapid screening tool, linked to this European data infrastructure, which could help with a diagnosis within minutes/hours and would guide therapeutic decisions.

A further important outcome would be the development of theranostics, with predictive biomarkers helping to stratify patients. By further developing and giving access to a wide variety of datasets, stratified therapies can become a reality whereby diagnostic information is fed into the system by clinicians, along with other key data, to produce recommendations for patient-specific treatment.

The multidisciplinary effort should be coalesced into a systems infection network, including not only clinicians, but also experts in data visualisation. This is to enhance clinicians' ability to make use of all this data on offer, as well as to provide rapid access to relevant results. The network should also include computational experts and modellers. By integrating –omics and clinical data, and exploiting high throughput molecular diagnostic, significant progress could be made.

New drugs should be developed utilizing specific low molecular weight compound libraries, though buy in from the pharmaceutical industry will be necessary. There should be linked efforts in molecular engineering and reverse engineering to develop these. In the long term, all this will result in less drug redundancy as well as less redundant therapy.

Summary

Infectious diseases

Needs

- ▶ Diagnostic challenge: well-established phenotypes are not available making early, accurate decision-making difficult
- ▶ Clinical data: lack of standardised, high quality and exchangeable data
- ▶ Translation of research into policy is a slow and difficult process, and can hinder efforts to tackle potential disease threats such as pandemics
- ▶ Anti-infective resistance is one of the biggest single issues faced in the field of infectious disease, causing the redundancy of previously effective drugs

Opportunities for Systems Medicine

- ▶ Global market for tackling anti-infective resistance as well as public understanding of issue
- ▶ Field includes a wide variety of stakeholders, from patients and clinicians to researchers, the pharmaceutical and medical device industry, regulators, health care and research funders. Systems Medicine could bring these groups together under one banner.
- ▶ Infectious diseases are often not treated with novel drugs; would benefit from Systems Medicine's emphasis on repositioning of existing drugs
- ▶ The use of omics data for diagnosis could provide a high impact. Examples here are the use of mass

spectrometry signatures and genomics to distinguish between species.

Short term

- ▶ Creation of standardised electronic health records for patient data approach
- ▶ Use of omics data for diagnosis
- ▶ Computational systems chemistry to be deployed in antibiotic discovery

Medium term

- ▶ Development of patient phenotyping tools, allowing diagnosis and response prior to the disease, rather than the current reactive response to outbreaks patients
- ▶ Series of small and focused multidisciplinary research initiatives incorporating clinicians, researchers and industry to focus on anti-infective resistance
- ▶ Creation of pan-European infrastructure for data collection, storage and exchange providing access to centralised high quality bioinformatics databases, including longitudinal data
- ▶ Development of theranostics, with predictive biomarkers helping to stratify patients

Long term

- ▶ Development of new antibiotics, requiring new bacterial focused compound libraries.
- ▶ Development of bedside rapid screening tool, linked to European data infrastructure, providing diagnosis within minutes/hours to guide therapeutic decision-making.
- ▶ Further research on the links between infection and chronic health through implementation of patient phenotyping.
- ▶ Implementation of early warning systems for pandemic outbreaks utilising the multidisciplinary expertise of Systems Medicine
- ▶ Multidisciplinary effort to be coalesced into a systems infection network

Systems Medicine for Public Health

State of the art: The round table employed the longstanding definition of public health, “the science and art of preventing disease, prolonging life and promoting health through the organized efforts and

informed choices of society, organizations, public and private, communities and individuals”²⁷. Public health necessarily addresses groups of individuals, rather than individuals, stratifying populations by risk factors. The population in question can be as small as a handful of people or as large as all the inhabitants of several continents (for instance, in the case of a pandemic).

The focus of a current public health intervention is to prevent and manage diseases, injuries and other health conditions through surveillance of cases and the promotion of healthy behaviour, communities and environments. This emphasis on prevention links in with the central tenets of P4 medicine, core to the systems approach, which advocates a model of medicine that is predictive, preventive, personalized and participatory.

Prevention strategies in public health are commonly defined as being three tiered:

1. *Primary prevention:* Primary prevention strategies emphasise general health promotion and risk factor reduction, and other protective health measures. Simplistically, these strategies are aimed at healthy groups of the target population to maintain their good health. Strategies can include health education and health promotion programmes designed to foster healthier lifestyles and environmental health programmes designed to improve environmental quality.
2. *Secondary prevention:* Secondary prevention focuses on early detection and swift treatment of disease. Its purpose is to cure disease, slow its progression, or reduce its impact on individuals or communities. A common approach to secondary prevention is screening for disease, such as the non-invasive computerized test for the early detection of heart disease.
3. *Tertiary prevention:* Tertiary Prevention strategies involve both therapeutic and rehabilitative measures once disease is firmly established. Examples include treatment of diabetics to prevent complication of the disease and the ongoing management of chronic heart disease patients with medication, diet, exercise, and periodic examination.

²⁷ Winslow, Charles Edward Amory, The Untilled fields of public health. *Science* . 1920 ([Article](#))

Needs: Many strategies in public health focus on secondary and tertiary prevention, and are deployed in a reactionary and reductionist manner, tackling individual concerns such as physical activity, diet, smoking, alcohol, drugs, sexual health, violence and injury, mental health and air pollution rather than adopting a holistic approach. In light of the current focus of public health strategies on secondary and tertiary prevention, it was suggested that Systems Medicine could have a high impact by addressing primary prevention (as already carried out in EU vaccination and health programmes).

The breadth of the field of public health was highlighted as a major issue, containing within it many disparate challenges. Prevention requires a long term approach as well as cultural changes and is linked to issues such as educational and socio-economic status of individuals.

A recurring theme was the importance of patient empowerment and public engagement. Top down public healthcare strategies can appear overly didactic and prescriptive; ensuring the involvement of the public and the patient in decision making processes from the start can lead to better outcomes and higher impacts of policies. A related opportunity that was highlighted was the growth of options for patients to treat and take measurements from themselves, making them an active participant in their own treatment rather than the passive recipient of traditional paradigms.

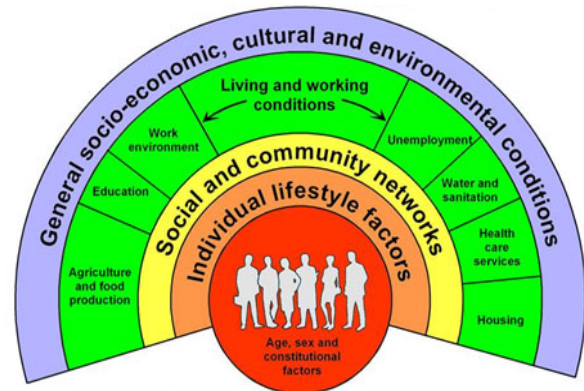
The politicized nature of debates related to public health was recognized as a considerable challenge. Political priorities for health vary across Europe and are influenced by a range of factors, from population demographics to government election cycles. Thus, to ensure significant results, consensus on public healthcare priorities is required at a European level.

The breadth of this field also incorporates issues such as economics costs of health insurance system, the social context of individuals, health inequalities, and the complex issue of comorbidities in patients.

Opportunities for Systems Medicine: At first sight, it was suggested that public health and Systems Medicine seem an unlikely fit, with the former's emphasis on broad population-based solutions as opposed to the latter's focus on greater personalization of medicine. However, the necessity for stratification of approaches to tackle different problems and issues as required by public health can and should be informed by the intelligent design that Systems Medicine approaches can offer.

A systems approach is well-placed to build on the existing social model of public health (illustrated below

in Dahlgren and Whitehead's policy rainbow²⁸, Fig. 6) which emphasises the relationship between the individual, their environment and their health.



Source: Dahlgren and Whitehead, 1991

Figure 6: Social model of public health.

Individuals are at the centre of this conception while surrounding them are influences on health that can be modified. The first layer is personal behaviour and ways of living that can promote or damage health. The next layer is social and community influences, which provide mutual support for members of the community in unfavourable conditions. The third layer includes structural factors such as housing, working conditions, access to services and provision of essential facilities.

The round table identified participatory prevention as a key opportunity for Systems Medicine, with a focus on primary prevention. This kind of citizen participation, whereby the patient and society as a whole is empowered through involvement in decision making processes, can reap considerable rewards. The example of SugarPal Diabetes Manager was cited, whereby diabetes patients can use a smart phone application to record and calculate insulin and blood sugar levels, simultaneously taking the guesswork out of blood sugar management and empowering the patient.

The utilization of systems methods such as the modelling of longitudinal data on key population groups was seen as a major opportunity and potential benefit of this approach. An assets perspective which focuses on healthy ageing and health equality should be employed, along with an integrative approach of health factors and co-morbidities.

Strategy / implementation: The round table participants identified a series of key actions to develop

²⁸Dahlgren, G and Whitehead, M (1991) Rainbow model of health in Dahlgren, G (1995) European Health Policy Conference: Opportunities for the future. Vol II – Intersectoral Action for Health. Copenhagen: WHO Regional Office for Europe.

participatory prevention, with a focus on primary prevention, utilizing a Systems Medicine approach.

In the short term, the systems approach to primary prevention and to public health more broadly needs to be clearly conceptualized, with the necessary tools, methodology and funding sources identified. This will require collaborations to be developed across the breadth of the stakeholder groups involved in public health, from public health providers and patient groups, to researchers, scientists, funders and industry.

The panel suggested that in the medium term, the validity of the toolkit and methodology identified in the first phase should be tested through pilot projects at community level. This would be beneficial in terms of encouraging the participatory approach central to Systems Medicine. The results of this piloting exercise would be expected to feed into public health policy at a European level.

It was suggested that the successful implementation of a systems approach could have far-reaching impacts on primary prevention in the long term, from positive behaviour change and improvements to population health and a wider paradigm shift from a reductionist to a holistic approach.

The strengths identified of a systems approach to primary prevention were its comprehensive, multidisciplinary and participatory focus which would mark a move away from the current reductionist strategies employed in the field. It is believed that there are significant opportunities in this approach, primarily the positive socio-economic impact of improved health for society and individuals. The panel highlighted the potential of influencing the European Commission's flagship Horizon 2020 funding programme as a major opportunity for securing support for this initiative. Threats that were identified to the implementation of the systems approach were data availability, the difficulty of engaging stakeholders, the costs of initiating such a paradigm shift, as well as the complexity of public health issues. There also remained concerns that public health and Systems Medicine did not appear to be natural bedfellows.

The panel suggested that this implementation process outlined would result in the development of a framework for Systems Medicine based public health and a wider paradigm shift for public health as a whole. The socio-economic impacts and health benefits would be felt by individual citizens and society as a whole.

Summary

Systems Medicine for public health

State of the art

- ▶ “The science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals” (Winslow, 1920).
- ▶ Addresses groups of individuals, stratifying populations by risk factors.
- ▶ Focus of a current public health intervention is to prevent and manage diseases, injuries and other health conditions through surveillance of cases and the promotion of healthy behaviour, communities and environments, linking to the central tenets of P4 medicine, core to the systems approach.
- ▶ Three tiers of prevention strategies:
- ▶ Primary prevention: emphasise general health promotion and risk factor reduction, and other protective health measures.
- ▶ Secondary prevention: focuses on early detection and swift treatment of disease tertiary prevention
- ▶ Tertiary prevention: therapeutic and rehabilitative measures once disease is firmly established.

Needs

- ▶ Current strategies focus primarily on secondary and tertiary prevention, and are deployed reactively
- ▶ Prevention requires a long term approach as well as cultural changes and is linked to issues such as educational and socio-economic status of individuals
- ▶ Importance of patient empowerment and public engagement – bottom up approach
- ▶ Consensus on public healthcare priorities is required at a European level, but difficult to achieve.

Opportunities for Systems Medicine

- ▶ Necessity for stratification of approaches to tackle different problems can be informed by the intelligent design that Systems Medicine approaches offer
- ▶ Participatory prevention: citizen and society as a whole empowered by involvement in decision making processes
- ▶ Modelling of longitudinal data on key population groups

- ▶ Integrative approach of health factors and co-morbidities

Short term

- ▶ Conceptualisation of systems approach to primary prevention, with the necessary tools, methodology and funding sources identified
- ▶ Development of collaborations across stakeholder groups involved in public health, from public health providers and patient groups, to researchers, scientists, funders and industry

Medium term

- ▶ Validification process of toolkit and methodology identified in the first phase through pilot projects at community level, encouraging the participatory approach central to Systems Medicine
- ▶ Results of piloting exercise feed into public health policy at a European level

Long term

- ▶ Positive behaviour change in primary prevention
- ▶ Improvements to population health
- ▶ Wider paradigm shift from a reductionist to a holistic approach

Additional application examples

Relevant publications for Systems Medicine (suggested by the reviewers of this document)

Using a network model to predict epidemics

1. Brockmann and Helbing: The Hidden Geometry of Complex, Network-Driven Contagion Phenomena; Science (2013) [[PDF](#)]
2. Mapstone M et al.: Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med (2014) [[PubMed](#)]

Using a model-based closed-loop treatment

1. El-Khatib et al.: A Bihormonal Closed-Loop Artificial Pancreas for Type I Diabetes; Sci Transl Med (2010) [[PubMed](#)]

2. Méndez and Femat: Mechanisms of prion disease progression: a chemical reaction network approach. IET Syst Biol (2011) [[PubMed](#)]

3. Woodcock and Woosley. The FAD critical path initiative and its influence on new drug development. Annu Rev Med (2008) [[PDF](#)]

Novel training approach

1. Voit et al.: A feel for systems; Mol Sys Biol (2012) [[PDF](#)]

Reviews Systems Medicine

1. Opinion - Bock and Lengauer: Managing drug resistance in cancer: lessons from HIV therapy. Nature Reviews Cancer (2012) [[PDF](#)]
2. Villoslada et al.: Systems biology and its application to the understanding of neurological diseases. Ann Neurol (2009) [[PubMed](#)]
3. Villoslada and Baranzini: Data integration and systems biology approaches for biomarker discovery: challenges and opportunities for multiple sclerosis. J Neuroimmunol (2012) [[PubMed](#)]
4. Tegnér et al: Computational disease modeling -fact or fiction? BMC Syst Biol (2009) [[PDF](#)]
5. Gibbs: Medicine gets up close and personal. Nature 2014 [[PubMed](#)]
6. Schadt and Bjorkegren: NEW: network-enabled wisdom in biology, medicine, and health care. Science translational medicine 2012 [[web link](#)]

Original articles Systems Medicine

1. Martinez-Pasamar et al: Dynamic cross-regulation of antigen-specific effector and regulatory T cell subpopulations and microglia in brain autoimmunity. BMC Syst Biol (2013) [[PDF](#)]
2. Vélez de Mendizábal et al.: Modeling the effector - regulatory T cell cross-regulation reveals the intrinsic character of relapses in Multiple Sclerosis. BMC Syst Biol (2011) [[PDF](#)]
3. Pertsovskaya I et al.: Transient oscillatory dynamics of interferon beta signaling in macrophages. BMC Syst Biol; 7:59 (2013) [[PDF](#)]

4. Goñi J et al.: The semantic organization of the animal category: evidence from semantic verbal fluency and network theory. *Cogn Process* (2011) [[PDF](#)]
5. Martínez-Forero et al.: Steady state detection of chemical reaction networks using a simplified analytical method. *PLoS One* (2010) [[PDF](#)]
6. Goñi J et al.: A computational analysis of protein-protein interaction networks in neurodegenerative diseases. *BMC Syst Biol* (2008) [[PDF](#)]
7. Palacios et al.: A network analysis of the human T-cell activation gene network identifies JAGGED1 as a therapeutic target for autoimmune diseases. *PLoS One* (2007) [[PubMed](#)]
8. Bangs A. Predictive biosimulation and virtual patients in pharmaceutical R and D. *Stud Health Technol Inform* (2005) [[PubMed](#)]
9. McShane et al.: Criteria for the use of omics-based predictors in clinical trials. *Nature* 2013 [[PubMed](#)]
10. Barrenas et al.: Highly interconnected genes in disease-specific networks are enriched for disease-associated polymorphisms. *Genome biology* 2012 [[PubMed](#)]
11. Gustafsson et al.: Integrated genomic and prospective clinical studies show the importance of modular pleiotropy for disease susceptibility, diagnosis and treatment. *Genome Med* 2014 [[PubMed](#)]
4. Wu: Dynamics Modeling as a Weapon to Defend Ourselves Against Threats from Infectious Diseases and Bioterrorist Attacks. *SAMSI* (2011); PPT presentation: [http://www.samsi.info/sites/default/files/Wu_february2011.ppt]
5. Denny et al.: Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nature biotechnology* 2013 [[web link](#)]
6. Lippert et al.: A mechanistic, model-based approach to safety assessment in clinical development. *CPT Pharmacometrics Syst Pharmacol*. 2012 [[PubMed](#)]
7. Krauss et al.: Integrating cellular metabolism into a multiscale whole-body model. *PLoS Comput Biol*. 2012 [[PubMed](#)]

Cancer medicine example (personalized)

Original articles electronic medical records analysis and algorithms

1. Martínez-Lapiscina et al.: Is the incidence of optic neuritis rising? Evidence from an epidemiological study in Barcelona (Spain) 2008-2012. *J Neurol* (2014) [[PubMed](#)]
2. Velez de Mendizabal et al.: Predicting relapsing-remitting dynamics in multiple sclerosis using discrete distribution models: a population approach. *PLoS One*. (2013) [[PDF](#)]
3. Bejarano et al.: Computational classifiers for predicting the short-term course of Multiple sclerosis. *BMC Neurol* (2011) [[PDF](#)]
1. Faratian et al.: Systems Biology Reveals New Strategies for Personalizing Cancer Medicine and Confirms the Role of PTEN in Resistance to Trastuzumab. *Cancer Res* (2009) [[PDF](#)]
2. Neal et al.: Response Classification Based on a Minimal Model of Glioblastoma Growth Is Prognostic for Clinical Outcomes and Distinguishes Progression from Pseudoprogression. *Cancer Res* (2013) [[PDF](#)]
3. Wiens et al.: Luminal subtypes predict improved survival following central nervous system metastasis in patients with surgically managed metastatic breast carcinoma. *Arch Pathol Lab Med* (2014) [[PubMed](#)]
4. Lévi: The circadian timing system: a coordinator of life processes: chronobiological investigations. Implications for the rhythmic delivery of cancer therapeutics. *IEEE Eng Med Biol Mag* (2008) [[PubMed](#)]
5. Taylor et al.: Dynamic modularity in protein interaction networks predicts breast cancer outcome. *Nature biotechnology*. 2009 [[PubMed](#)]
6. Jörnsten et al.: Network modeling of the transcriptional effects of copy number aberrations in glioblastoma. *Molecular systems biology* 2011 [[PubMed](#)]

7. Huttenhain et al.: Reproducible quantification of cancer-associated proteins in body fluids using targeted proteomics. Science translational medicine 2012 [[PubMed](#)]
8. Lee et al.: Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. Cell 2012 [[PubMed](#)]
8. Drukker et al.: Mammographic screening detects low-risk tumor biology breast cancers. Breast Cancer Res Treat (2014) [[PubMed](#)]
9. The Mammaprint® - Test system that is able to predict therapeutic outcome in breast cancer patients using patterns of gene expression and predetermined mathematical algorithms [[web link](#)]

Epidemiology resources indicating the impact of math modelling

1. Scientific Pandemic Influenza Subgroup on Modelling [[web link](#)]
2. Centre for Continuing Professional Development; Imperial College London [[web link](#)]

Successful example of personalised medicine based on the genomic analysis

1. Hidalgo M, et al.: Personalizing Cancer Treatment in the Age of Global Genomic Analyses: PALB2 Gene Mutations and the Response to DNA Damaging Agents in Pancreatic Cancer. Mol Cancer Ther (2011) [[PDF](#)]
2. Valencia and Hidalgo: Getting personalized cancer genome analysis into the clinic: the challenges in bioinformatics. Genome Medicine (2012) [[PDF](#)]
3. SYSTHER: Successful implementation of a bi-national virtual institute with database implementation, and common projects of clinicians, researchers and theoretical scientists [[web link](#)]
4. Article NY Times - In Treatment for Leukaemia, Glimpses of the Future [[web link](#)]
5. Hector et al.: Clinical application of a systems model of apoptosis execution for the prediction of colorectal cancer therapy responses and personalisation of therapy. Gut (2012) [[PubMed](#)]
6. Vainas et al.: Personalising docetaxel and G-CSF schedules in cancer patients by a clinically validated computational model. Br J Cancer (2012) [[PubMed](#)]
7. Kogan et al.: Reconsidering the paradigm of cancer immunotherapy by computationally aided real-time personalization. Cancer Res (2012) [[PubMed](#)]
10. Hood et al.: Collection of articles and initiatives. [[PubMed](#)]
11. Snyder et al.: Collection of 'omics and systems diagnostics articles and initiatives. [[PubMed](#)]
12. BMBF/CancerSys Treat20 project. [[web link](#)]
13. Kuhn et al.: Systematic identification of proteins that elicit drug side effects. Molecular systems biology 2013 [[PubMed](#)]
14. McKinney et al.: A CD8+ T cell transcription signature predicts prognosis in autoimmune disease. Nature medicine 2010 [[PubMed](#)]
15. Okada et al.: Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 2014 [[PubMed](#)]
16. Bruhn et al.: A Generally Applicable Translational Strategy Identifies S100A4 as a Candidate Gene in Allergy. Science translational medicine 2014 [[web link](#)]

Annex III: Overview of current initiatives and plans on the national level

BMBF, Germany

BMBF invested some 435 M€ over the last 10 years in quite a high number of initiatives on Systems Biology. Several of these initiatives have addressed clinical topics and have been focused on basic research on diseases. These initiatives have paved the way for the implementation of Systems Medicine in Germany. With the recently launched novel concept “*Paving the Way for Systems Medicine – The e:Med research and funding concept*”, the BMBF puts a clear focus on translational research towards clinical practice and the patient. Up to now BMBF is the only European funding body who developed a far reaching and precise strategic agenda for Systems Medicine containing well-structured research programs.

The e:Med research and funding concept: This initiative will lead to funding Systems Medicine in five modules and will amount to a financial investment of 200 M€ within a time period of 8 years ([e:Med concept](#), PDF).

- ▶ Module I: Systems Medicine Research Consortia
- ▶ Module II: Demonstrators for an Individualized Medicine
- ▶ Module III: Young Scientists
- ▶ Module IV: Future-oriented and Cross-cutting Measures
- ▶ Module V: Internationalization

The e:Bio innovation competition program in Systems Biology: The e:Bio initiative aims at starting novel innovative approaches in Systems Biology in order to solve societal challenges. e:Bio bundles Systems Biology funding under a one roof concept containing four distinct modules (funding volume 100 M€ between 2012-2020).

- ▶ Module I: Ideas Competition National (bottom-up approach)
- ▶ Module II: Transfer (from Basic Research to Clinical and Economical Applications)
- ▶ Module III: Young Scientists
- ▶ Module IV: Ideas Competition International (bottom-up approach, transnational consortia such as ERASysAPP and ERASynBio)

The Virtual Liver Network (VLN): VLN aims at a dynamic mathematical model that represents, rather than fully replicates human liver physiology, morphology and function, integrating quantitative data from all levels of organization, from sub-cellular levels to the whole organ and how this is disturbed in disease ([website](#)).

CancerSys – Systems Biology of Cancer: CancerSys aims at causing a paradigm shift from universal standard treatment to individualized treatment by utilizing the potential of systems biology for cancer research, at supporting the development of new drugs with the help of predictive models, and at using new activation profiles (transcriptomes, proteomes) and biomarkers for early diagnosis methods as well as laboratory and pharmacogenetic diagnostics ([website](#)).

MedSys – Medical Systems Biology: MedSys aims at a better understanding of complex diseases through an integrative Systems Biology approach to gain a deeper understanding of pathophysiological mechanisms that causes the course and the regulation of disease ([website](#)).

GerontoSys – Systems Biology of Aging: GerontoSys aims at elucidating key processes of aging and age-related diseases through a Systems Biology approach in order to accelerate applied medical research, basic research and research with focus on prevention, regeneration as well as translation ([website](#)).

PtJ/Pt-DLR, Germany

The Project Management Jülich has been heavily involved in Systems Biology programmes, both on a national and international level. The novel e:Med programme is carried out in conjunction with the Project management DLR. In all programmes the contracting body is BMBF.

FNR (Luxembourg)

FNR recently launched a pilot call on Systems Medicine - National Centre of Excellence in Research on the topic of Early Diagnosis and Stratification of Parkinson's Disease ([NCER 2013 call](#)). Participation is also within BMBF/e:Med in Module I with a budget of up to 2M€ to support the Luxembourgish partners in German-Luxembourgish consortia.

Luxembourg Centre for Systems Biomedicine, Luxembourg

The LCSB is an interdisciplinary research centre at the University of Luxembourg. It focuses on closing the link

between systems biology and medical research in order to accelerate biomedical research. Collaboration between biologists, medical doctors, computer scientists, physicists and mathematicians at the LCSB offers new insights in complex systems like cells, organs, and organisms. These insights allow understanding of principal mechanisms of disease pathogenesis and are essential for developing new tools in diagnostics and therapy.

ZonMw and NWO, the Netherlands

The Netherlands have launched a call for centres of excellence in the field of systems biology (2009, total budget of 13.5 M€ ([website](#))). The three highest ranking and thus awarded centres conduct research with relevance for the field of medicine.

Cancer Systems Biology Centre (CSBC; [website](#)) is based within the Netherlands Cancer Institute / Antoni van Leeuwenhoek hospital. Within the CSBC, research groups work together to develop a strategy to tackle the complexity of molecular networks that govern breast tumorigenesis, with the goal to deliver improved diagnostic tools to enable tailored cancer therapy.

Centre for Systems Biology and Bioenergetics (CSBB; [website](#)) consists of more than 35 different research groups of the Radboud University and Nijmegen University Medical Centre. They work together to model mitochondrial energy production, distribution and expenditure in the context of human disease.

The Systems Biology Centre for Metabolism and Ageing (SBC-EMA; [website](#)) is a joint effort between the University Medical Centre and the university Groningen ([website](#)). The centre also focuses on the energy metabolism, but its emphasis is on ageing.

These three centres operate in close interaction with the SB@NL, the platform for Systems Biology in the Netherlands ([website](#)), facilitating training and development of modelling and systems analysis tools and approaches to be used in biomedical research, agricultural biotechnology and microbial biotechnology.

The ministry of Health, Israel

Funds biomedical research with no specific focus but based on quality assessment. Personalized medicine is becoming more important.

SystemsX.ch, Switzerland

The Swiss initiative SystemsX.ch focuses on systems biology and systems approaches. It's not specifically focused on Medical Systems Biology or Systems Medicine, but it can fund research projects in the field of Systems Medicine ([website](#)). In 2014/2015 a call for proposals is planned especially with focus on Systems Medicine. Additionally, SystemsX.ch together with the Swiss Institute of Bioinformatics (SIB) are organizing a joint summer school in July 2014 with the topic: "Systems Medicine and its Applications". SystemsX.ch will end in 2016 and may be followed up by an initiative that is more focused on the area of Systems Medicine or personalized medicine. The aim is to combine systems approaches into the public health system.

Ministry of Education, Science and Sport (MIZS), Slovenia

The MIZS doesn't have priorities or a specific focus on Systems Medicine. One reason is that Slovenia is a small country with a broad diversity of scientific areas, so the budget will not be strictly defined. There are mainly open calls instead of focussed calls. However, health and biotechnology are priorities. Internationally, MIZS has funded Systems Biology projects with a medical relevance in the ERASySBio-plus call (2010) and recently in the TRANSCAN call "Validation of biomarkers for personalized cancer medicine".

The Research Council of Norway, RCN

RCN covers all aspects of science and for 2014 the areas highlighted are: Active and healthy ageing, energy, bio resources, climate, business development, infrastructure, internationalisation, recruitment. Among the projects funded will be projects that could be defined as Systems Medicine.

The Biotechnology for Innovation program (BIOTEK2021) is working on a strategy to develop systems biology the coming years. Systems Medicine will be part of this, but probably not as a separately focused area. This program started in 2012.

National Institute of Health Carlos III, Spain

ISCIII, Spain ISCIII is focussed on biomedical health research and has no focussed calls on specific topics. Personalized medicine will become more important for

the future. Now ISCIII is more involved in developing fields through collaboration on international initiatives (e.g. ERASySAPP, PARAMED).

Flemish government - department Economy, Science and Innovation (EWI)

The EWI co-ordinates the different agents of the Flemish government regarding economic, scientific and innovative domains. The funding is not specifically focused on a certain research area, but research has to match the criteria for excellence. The EWI is familiar with the term Systems Medicine, but there are no initiatives or funding programmes within the Flemish Government specifically focussed on Systems Medicine.

VIB (*Vlaams Instituut voor Biotechnologie*), funded by the EWI, is a life sciences research institute, based in Flanders. They perform basic research with a strong focus on translating scientific results into pharmaceutical, agricultural and industrial applications. The departments choose the focus of the research. The research field on systems biology is very successful and systems biology towards medicine is an emerging field.

There are several programmes focussed on systems biology towards personalized medicine:

- ▶ Plant Systems Biology department of VIB-Ugent ([website](#)).
- ▶ IWT, Agency for Innovation by Science and Technology: funding agency including channels for financing projects in Applied Biomedical research with a primary social purpose and the Transformational Medical Research (TGO, [website](#))

First conclusions and future work

In conclusion, there is an increasing interest in and awareness of Systems Medicine among funding organisations across Europe. So far, two new, large-scale initiatives in Germany and Luxembourg are specifically focused on Systems Medicine. Other countries, like the Netherlands, Israel, Spain, Slovenia, Belgium and Norway do not (yet) invest specifically in Systems Medicine initiatives. Nevertheless all interviewed organisations have invested in large-scale initiatives on SysMed-related topics (e.g. Systems Biology, Translational Medicine) and occasionally fund

projects involving SysMed research within broad research calls. The Swiss initiative SystemsX.ch goes a step further than this and has organized a summer school on Systems Medicine and its Applications in 2014. This may pave the way for a new initiative that is more focused on Systems Medicine/personalized medicine.

Current plans of public and private funders for pan-European cooperation in supporting systems medicine approaches:

- ▶ **New ERA-Net:** Several European funders are interested to set up an ERA-Net on Systems Medicine. The ERA-Net will create a first basis to create pan-European Systems Medicine research programmes on a bigger scale beyond bi-lateral programmes. The ERA-Net is intended as a test bed to assess the potential of integrated European Systems Medicine initiatives.
- ▶ **European research framework:** Depending on the outcome of the ERA-Net, decisions will be made if a larger and more permanent framework of European countries in support of Systems Medicine will be established. A Joint Programming Initiative ([website](#)) is seen as a potential instrument for such a framework.

Annex IV: Key performance indicators

There is an initial requirement for investment in proof of concept projects that are driven by clinical needs and that demonstrate:

- ▶ The technological and methodological feasibility.
- ▶ Tangible clinical benefits.
- ▶ The social and economic benefits of Systems Medicine.

Because of the nature of Systems Medicine, these projects will be collaborative and interdisciplinary, and will need funding at European level.

Successful outcomes of proof of concept projects are necessary to encourage both buy-in by wider society (from the scientific/medical community to the patient) and further investment into Systems Medicine by large pharmaceutical companies and SMEs.

Details of what a good Systems Medicine proof of concept should entail will be provided as a specific set of performance indicators below.

What characterizes a (good) Systems Medicine project or proposal?

1. **Concept:** Systems medicine is a conceptual approach to solving significant and economically important clinical questions. It may be applied to many areas, including the incorporation of personalised medicine and integration of –omics data, but as a concept it goes far beyond either of these two examples in order to use systems thinking to model and implement change.
2. **Healthcare:** Systems medicine addresses major healthcare issues including where a societal rather than merely a personalised approach is needed, such as co-morbidity in ageing, chronic disease management in the community, the application of technology for remote patient monitoring, policy development and European wide co-ordinated planning for health.
3. **Clinical:** Systems medicine must deliver something clinically useful. It is not about data generation or gathering, it is about novel use of data. Applications almost always will be cross disciplinary and collaborative.

4. **Novelty:** Systems medicine should not be viewed as simply a re-labelling of funding streams, but a deliberately high setting of a new bar where impact is more than traditional academic measures of success, acknowledging the urgency of the problems and the essential requirement to appropriately incentivise open collaboration.

Evaluation criteria

General

- ▶ The proposed science should be internationally competitive
- ▶ Projects should identify and clearly state a focused clinical problem.
- ▶ Projects should strive beyond the current state-of-the-art and propose and form new, innovative concepts.
- ▶ The project should involve medical centres with focus on Systems Medicine
- ▶ The project should address the objectives of Systems Medicine:

Systems Medicine is the implementation of Systems Biology approaches in medical concepts, research and practice. This involves iterative and reciprocal feedback between clinical investigations and practice with computational, statistical and mathematical multiscale analysis and modelling of pathogenetic mechanisms, disease progression and remission, disease spread and cure, treatment responses and adverse events as well as disease prevention both at the epidemiological and individual patient level.

As an outcome Systems Medicine aims at a measurable improvement of patient health through systems-based approaches and practice.

- ▶ These concepts should comprise a Systems Medicine approach and the project should benefit from this approach. In other words: *the systems approach should help address questions that without the approach would remain unanswered.*

Clinical focus

- ▶ Projects should demonstrate a direct benefit to patients and the potential impact on clinical practice.
- ▶ The project should address significant clinical relevance with regards to the development of an

individualised therapeutic concept or the development of new drugs and/or the use of biomarkers for early diagnosis methods as well as laboratory/pharmacogenetic diagnostics and/or identification of new activation profiles (-omics approaches)

- ▶ The project should address topics related to the key processes of affecting a paradigm shift from standard (reactive) medicine to P4 (participatory, preventive, predictive and personalized) medicine employing a systems approach

Integration aspects: Composition of the consortium

- ▶ The partners should have the expertise to build up an interdisciplinary project
- ▶ There should be clear leadership
- ▶ Systems Medicine projects will typically involve a range of different expertise. Projects therefore require a project management structure adequate for multi and interdisciplinary teams.
- ▶ The composition of the consortium should be adequate to promote an integrated interdisciplinary programme: explain
- ▶ The composition of the involved partners should be adequate to guarantee economic exploitation: explain?
- ▶ Projects should have network activities and present ideas to create synergies among groups, possibly training.
- ▶ The integration of basic research and clinical practice should be sufficiently clarified; for instance there should be basic research available to back up the potential of a prognostic or diagnostic biomarker.
- ▶ Similarly, there should be an appropriate balance and integration of theory, modelling and experimentation, with a clear focus.
- ▶ The integration of existing data and newly generated data should be explained.
- ▶ Proposals should clearly state the data and experiments required, and clarify the access and availability of data vs. data that have to be generated
- ▶ The infrastructural conditions and technical know-how should be ensured for the usage of modern high-throughput technologies for large-scale data generation (e.g. -omics techniques) in combination with a Systems Medicine approach to address a clear medical question.

- ▶ Similarly, all types of data analyses and mathematical modelling, software tools should be clearly stated.

Sufficient validation

- ▶ Projects should clearly describe their strategy to validate the outcomes of the project, including the validation of the developed in silico models with experimental and clinical data

Data management and data standardisation

- ▶ The standardisation of data (acquisition/exchange) should be ensured and clearly described within the collaboration
- ▶ The project should take already existing data management concepts for Systems Medicine research into account
- ▶ The project management plan should reach out for an optimal data/material exchange

Availability of clinical material

- ▶ The collections of clinical material (cells, tissue, blood, DNA, and, if required, whole organs, etc.) and the associated clinical data of the test persons (patient cohorts with comprehensive clinical characterization) should be available and accessible

Transfer

- ▶ The concept should be qualified for applications in the biotechnological or biomedical areas
- ▶ The plan for the utilization, especially the economic exploitation, of results should be considered and well defined

Types of projects

- ▶ Truly new consortia with an innovative approach.
- ▶ Stratification of patient groups.
- ▶ Hypothesis-driven research; systems approaches.
- ▶ Biomarker discovery and patient signatures.
- ▶ Type of approaches: application vs. development of statistical approaches, construction of mechanistic dynamical models, machine-learning techniques.
- ▶ Focus software development vs. algorithms and models.
- ▶ Using (and adapting) existing tools vs. novel approaches.

Annex V: EU support and successful projects

European Commission strategic support towards Systems Medicine

To meet the technological and knowledge-based key challenges that still segregate Systems Medicine from medical applications, the European Commission has, since 2004, already funded 73 health projects (25 in FP6 and 48 in FP7) and allocated €415M for research, training and infrastructure in system biology. The main themes covered are addressing basic biological processes, bacteria, yeast, mammalian cells and diseases. These pioneering studies, involving an increasing number of SMEs, have led to encouraging results, globally recognized, that are propelling one of the ambitious HORIZON 2020 objectives which ultimately consists in building the European strategy for Systems Medicine.

Main EU success stories Systems Medicine

As previously emphasised, there are a wide range of European Commission supported projects ongoing which will ultimately enable patients and clinicians to benefit from the exploitation of Systems Medicine's potential. Demonstrator projects for data management and processing, proof of concepts projects (modelling networks nodes, *in silico* tools, etc.), knowledge-based projects (deciphering pathological pathways), infrastructure development projects as well as educational projects and coordinating projects are parts of these patient-driven initiatives. Following are three examples of projects with major economical, societal and scientific impact, followed by a list of projects current and recently supported by the European Commission in Systems Medicine.

APO-SYS: Apoptosis Systems Biology Applied to Cancer and Aids [\[more\]](#)

- ▶ 23 partners
- ▶ €11M in EC funding
- ▶ February 2008-January 2012

The APO-SYS consortium focused on delivering major progresses in comprehension of apoptosis (and more

generally cell death) in human diseases, by combining a series of Systems Biology approaches, *in silico*, *in vitro* (in organello and in cellula), *in vivo* and by integrating experimental results with large data sets acquired on tissue samples from patients suffering from diseases that are caused by deregulated apoptosis, in particular cancer and AIDS.

This project delivered significant advances in the comprehension of cell death in human diseases, in particular cancer and AIDS. APO-SYS refined new cell death pathway models, optimized and calculated prognoses and predictive parameters for the diseases, developed new guiding strategies for the amelioration of existing treatments and identified novel targets for therapeutic modulation of apoptosis, suggested new nomenclature of cell death based on morphological and biochemical parameters, which was accepted by the scientific community and cited for more than 500 times in peer-reviewed scientific publications. The consortium members have published 512 scientific publications and have submitted and/or registered 16 patent applications. APO-SYS delivered advances to citizens since the consortium worked on issues that have major impact in the quality of diagnostic and treatment of cancer and AIDS and thus subsequently led to an increase in patient's quality of life.

SYSCILIA: A Systems Biology Approach to Dissect Cilia Function and Its Disruption in Human Genetic Disease [\[more\]](#)

- ▶ 16 partners
- ▶ €11M in EC funding
- ▶ June 2010-May 2015

The aim of SYSCILIA is to identify the molecular mechanisms characterizing cilium function, and the discrete perturbations associated with dysfunction caused by mutations in inherited ciliopathies via a Systems Biology approach. The overall objectives are to establish a new paradigm for the study and modelling of complex eukaryotic systems, understanding how systems perturbation contributes to the modulation of clinical phenotypes, while providing better understanding of ciliary processes in biology and their associated diseases.

So far, the project generated the largest integrated network of ciliary protein complexes to date. SYSCILIA carried out the systems integration and modelling of the first whole genome siRNA screen for ciliogenesis and variants from next-generation sequencing of ciliopathy patients boosting functional insights in ciliary and ciliopathy-associated pathways. The resulting “Gold standard” for genes in ciliopathies represents a step towards improved diagnostics. Altogether, these preliminary results provide the scientific rationale for targeted therapies as well as drugs repurposing screens to develop ciliotherapeutics. The consortium has already published over 50 publications in highly-ranked peer-reviewed scientific journals.

MULTIMOD: A Module-Based Translational Approach to Stratify Patients for Individualised Medicine [[more](#)]

- ▶ 6 partners
- ▶ €2.5M in EC funding
- ▶ Dec 2009-Dec 2013

The aim of MULTIMOD is to develop and apply methods to form multi-layer modules in a complex disease in order (i) to analyse the modules to ultimately understand disease mechanisms and individual variations, (ii) to find protein markers of those variations, (iii) to apply the markers diagnostically in an effort to predict treatment response, and iv) to make the resultant bioinformatics methods widely available in a standardized form (e.g., as web-based tools) in order to facilitate other studies of complex diseases. The project ended in 2012 and as a result the consortium developed a module-based method to stratify patients for individualised medicine. The method was demonstrated to be widely applicable to complex diseases. The project has also resulted in 33 collaborative publications in high-impact scientific journals.

Additional EU projects with relevance to Systems Medicine²⁹

Acronym	Full title
APO-DECIDE	Apoptosis Modelling for Treatment Decisions in Colorectal Cancer
APO-SYS	Apoptosis Systems Medicine applied to cancer and AIDS. An integrated approach of experimental biology, data mining, mathematical modelling, biostatistics, systems engineering and molecular medicine
ASSET	Analysing and Striking the Sensitivities of Embryonal Tumours
COMBI-BIO	Development of COMBINatorial BIOmarkers for subclinical atherosclerosis
COMBI-MS	A novel drug discovery method based on systems biology: combination therapy and biomarkers for Multiple Sclerosis
EURO-MOTOR	European multidisciplinary ALS network identification to cure motor neuron degeneration
INFECT	Improving Outcome of Necrotizing Fasciitis: Elucidation of Complex Host and Pathogen Signatures that Dictate Severity of Tissue Infection
ISD	Intelligent Surgical Device
LSE	Technology approach to generate innovative Kinase Inhibitor Drugs
METACARDIS	Metagenomics in Cardiometabolic Diseases
MODHEP	Systems biology of liver cancer: an integrative genomic-epigenomic approach
MULTIMOD	Multi-layer network modules to identify markers for personalized medication in complex diseases
NEUROXSYS	Genomic Regulatory Systems of Human X-linked neurological diseases
PRIAT	Profiling Responders in Antibody Therapies
RESOLVE	A systems biology approach to RESOLVE the molecular pathology of two hallmarks of patients with metabolic syndrome and its co-morbidities; hypertriglyceridemia and low HDL-cholesterol
SYSCILIA	A systems biology approach to dissect cilia function and its disruption in human genetic disease
SYSCOL	Systems Biology of Colorectal Cancer
SysCLAD	Systems prediction of Chronic Lung Allograft Dysfunction
SysMalVac	Identifying correlates of protection to accelerate vaccine trials: systems evaluation of two models of experimentally-induced immunity to malaria
Sysmed IBD	Systems Medicine of chronic inflammatory bowel disease
SYSTEMCERV	Systems biology approaches to cervical pre-cancer and cancer
SYSTEMTB	Systems biology of Mycobacterium tuberculosis
WINTHER	WINTHERapeutics; development of a systems biology method to predict efficacy of cancer drugs to optimize individualized therapeutic decisions and improve clinical outcome for cancer patients

²⁹ Modified from the following webpage: European Commission, Research&Innovation, Health, [\[more\]](#)

Annex VI: Road Map Methodology

This road map was developed based on the input from a series of coordinated workshops and meetings throughout Europe attended by representatives from across our stakeholder groups. Semi structured roundtable discussions were organized around a number of specific topics, ranging from transversal methodological and infrastructural topics, to pathology centered, more applied discussions. The individual reports from these workshops can be found on www.casym.eu/publications.

The discussions were semi structured in that each round table had a chair plus one assistant to facilitate the discussion. The discussion was started by a short introduction reflecting the state of the art, given by the chair, followed by a brainstorming exercise to define specific priority areas. These were further ranked and the group discussed specific actions to be taken within a short, medium and long term time scale and performed a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis.

Round tables were driven using the following brainstorming methodology:

Step 1: Introduction

- ▶ Facilitator presents the methodology
- ▶ Leader asks who would be willing to be assistant, taking notes for wrap up
- ▶ Short presentation of each participant
- ▶ Leader present states of the art / issues

Step 2: Defining priority issues

- ▶ Discussion with participants on state of the art and priority issues
- ▶ Outcome: Shared diagnostic on state of the art and priority issue(s), 1 priority issue selected for discussion

Step 3: Brainstorming on actions

- ▶ Each participant identify 2-3 actions to tackle priority issue and present it to the round table (actions should take the form of a sentence composed of verb + complement)
- ▶ Leader, with help from participants, classifies actions (gathers similar actions)

- ▶ Leader, with help from participants, positions actions on the matrix (short, middle or long term / low middle or high impact)
- ▶ Step 4: Wrap up and detailing of 1st priority actions
- ▶ Expected outcomes are: Articulated actions positioned on a specific matrix and description of at least 1 priority action / recommendations

Annex VII: CASyM reports from stakeholder consultation events

The current document is the result of a broad stakeholder consultation process initiated by CASyM. Major tool of this ongoing process are focussed conferences and workshops with guided round table discussions (see above). The output of these events is summarized in specific reports and surveys (see below), which are the theoretical basis of the current roadmap and implementation strategy for Systems Medicine.

All reports are freely available for download from the CASyM website [[more](#)]:

1. From Systems Biology to Systems Medicine (Brussels, 2010).
2. EU/CASyM joint workshop (Brussels, 2012)
3. 1st open stakeholder consultation conference (Lyon, 2013).
4. 2nd clinically focused stakeholder conference (St Andrews, 2013).
5. Strategic modelling workshop (Heidelberg, 2013).
6. Systems Medicine training tutorial (Ljubljana, 2013).
7. Technological and ethical focused workshop (Lyon, 2013).
8. CASyM/ICSB2013 training workshop (Copenhagen, 2013).
9. Analysis of instruments for integrated research programmes (Luxembourg, 2013).
10. National programmes in Systems Medicine (December 2013)
11. Clinical needs in oncology and cardiovascular diseases as drivers for a Systems Medicine approach (Genoa, 2014)
12. Europe-wide inventory of industry involved in Systems Medicine (March 2014)

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