Paving the Way for Systems Medicine

The e:Med research and funding concept
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Executive Summary

**e:Med is a research and funding concept** that promotes systems-oriented research into diseases and preventive measures by linking life sciences with information sciences. As part of the Federal Government’s Health Research Framework Programme, e:Med focuses especially on the following fields of action: “Focussed research into major diseases”, “Individualised medicine”, “Research into prevention and nutrition” and “International cooperation in health research”. The primary objective of the effort is to establish systems medicine[^1] in Germany.

*Systems medicine uses systems-oriented approaches, in both research and clinical care, to illuminate complex physiological and pathological processes and, thereby, to create a basis for development of innovative therapies and preventive measures.*

In research into diseases and preventive measures, systems medicine’s holistic approach yields findings that are more comprehensive than those provided by consideration of isolated, individual aspects. For such an approach, systems medicine requires data that are both diverse in range and processed carefully with a view to specific applications. The data involved can range from genetic data to blood counts and x-rays. Today, the processes for generating comprehensive genetic, cell-biological, physiological and visual data sets are well established, and their costs are reasonable and continue to decrease. The key to their proper analysis lies in electronic processing (e:Med), i.e. computerised archiving, analysis and integration of data. And in those areas, mathematics and information sciences play a crucial role.

The e:Med research and funding concept especially supports study of the following types of questions: How do molecular networks function within the human body? What environmental factors influence them? How can the systems-oriented approaches used in biomedical research best be translated to clinical practice? To answer this question, methods and findings from basic research can be tested in clinical trials on small groups of patients.

Now, systems medicine research consortia are to be established, and pilot studies on individualised medicine carried out, with a view to achieving such aims. In the process, special emphasis will also be placed on promoting young scientists and on internationalisation, via active participation in international strategic research initiatives and major international research projects.

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[^1]: The EU Commission defines the term “systems medicine” relatively narrowly to mean “application of systems biology methods to medicine” (cf. CSA Systems Medicine). Within that understanding, the main emphasis is on mathematical modelling of complex biological processes. In the context of the e:Med concept, the term is used in a broader sense to mean not only application of “systems biology methods” but also, and more generally, application of systems-oriented approaches to medicine that facilitate holistic consideration of complex interrelationships.
1 Motivation and Objectives

Since the turn of the millennium, systems-oriented research approaches have been revolutionising biomedical research. In Germany, the BMBF acted early in launching funding priorities on genome research and systems biology, and thereby in contributing significantly to the structural and substantial establishment of those research fields. Now, after a decade of intensive further development, the time is ripe to apply those areas’ concepts and techniques to the major challenges in health research.

This process is being advanced especially by rapid technological progress throughout a broad range of pertinent analytical techniques, including genomics, proteomics and imaging methods. As the costs of relevant data generation and processing continue to fall, such techniques will be used routinely in clinical prediction, diagnosis and therapy of diseases. Experts now expect such techniques as cancer-genome analysis and multiparametric proteomics to become part of the standard medical repertoire within the next five to ten years.

With a view to promoting integration of these new technological and methodological approaches in clinical applications, for the benefit of patients, the BMBF is thus introducing a concept for establishing systems medicine in Germany. The concept is expected to enable systems-oriented medical research, efficiently linking mathematics and information science with clinical disciplines and life sciences, to yield findings of relevance for medical care and to provide a basis for application of such findings to clinical practice. These are the objectives to which the e:Med research and funding concept is committed.

1.1 Health policy challenges

Medical progress has significantly improved public health: Life expectancies have increased, and many diseases have lost their sting. These positive trends need to be continued. And they need to be continued in the face of three of the most important pertinent challenges in industrialised countries:

1.1.1 Common diseases on the rise as a result of demographic change

Increasing life expectancies, and profound changes in lifestyles and nutrition habits, have led to a higher prevalence of common diseases such as cardiovascular diseases, cancer and neurological and metabolic disorders. All such diseases have high socio-economic relevance and highly complex causes and courses. Because the factors leading to their occurrence are numerous, they often respond poorly to therapies that focus only on individual causes or symptoms.

1.1.2 Ineffective medicines and therapies

Today, even the best drugs are only effective for some patients; responder rates of 30 to 70 percent are reported, depending on the disease involved. A therapy’s effectiveness can differ widely from patient to patient, even with exactly the same diagnosis. This is because diagnoses are often based on just a few parameters – and fail to take account of decisive differences in individual patients’ cases.

This insight is the starting point for individualised medicine. In individualised medicine, more comprehensive and precise diagnostics enable better adaptation of available therapies to patients’ individual cases and needs. At the same time, this approach supports the development of new, more precise – and, thus, more effective – therapies.

1.1.3 How the environment and lifestyles influence health

The key factors that contribute to any person’s health include hereditary factors, environmental influences and lifestyle. It is now well established that sensible eating habits and lifestyles can indeed considerably reduce the risk of disease. Prevention definitely offers substantial chances. But to develop preventive and therapeutic measures against environment-related and nutrition-related diseases, we need a precise understanding of the way in which relevant pathophysiological processes and external factors interact.
1.2 The research-policy answer

The e:Med research and funding concept is aimed at application-oriented basic-research projects focusing on such challenges. In particular, it is oriented towards projects involving electronic data processing and integration (e:Med) – which paves the way for systems medicine.

1.2.1 Complex questions – systems-oriented answers

Research efforts carried out to date have highlighted mainly one major insight: the ways in which many diseases occur and develop can be understood only incompletely via isolated considerations of individual components and factors. When seen in individual cases, major common diseases have multifactorial causes and highly specific histories. On the one hand, diet, exercise and environmental factors play major roles. On the other, in any specific case, highly individual genetic and physiological processes, influenced by those factors, tip the balance towards health or sickness. Future research and funding activities will thus focus on the understanding of such complex interactions. How do the different levels of the overall system interact? What mechanisms play a role, and how can they be regulated?

Worldwide, there is agreement that further progress in preventing, detecting and treating common diseases will be made only by applying systems-oriented methods and technologies, as in state-of-the-art basic research in the life sciences, to medicine. The goal is thus to broaden classical medicine to include systems medicine.

Systems medicine research approaches are being driven by dynamic technological advances in the life sciences. Such advances especially include major improvements in techniques for collecting and processing large sets of genetic, cell-biological, physiological and visual data, at ever-lower related costs.

The so-called omics technologies (“genomics”, “proteomics”, “metabolomics”) have now made it possible to simultaneously analyse all of the molecules of certain classes, such as DNA, proteins or metabolites, involved with reference to an entire system. The resulting enormous volumes of medically relevant data can be analysed, integrated and applied only with the help of state-of-the-art information technologies.

In the field of systems biology, researchers are pursuing an approach involving quantitative description, with sharp chronological resolution, of interactions of factors in living systems, with a view to predicting factors’ development. As a result, in the future, computer simulations could well be able to predict the probabilities for the occurrence of diseases and for the possibilities of curing them.

Such research approaches are the basis of systems medicine. They promise to provide new insights into the causes of diseases and to open up new perspectives for preventing and curing diseases. And such progress will be significant especially with regard to individualising prevention and treatment strategies.

1.2.2 The funding objectives of e:Med

- With this orientation, e:Med seeks to pave the way for the establishment of systems medicine in Germany. In the process, it will aim to help enhance our understanding of molecular networks, of their functions in the human body and of the way in which they are influenced by environmental factors. It will place special emphasis on integrating different levels of knowledge – for example, on linking the findings produced by different “omics” analyses.
- State-of-the-art information technologies and innovative data management need to play an even more important role in disease-oriented research. Systems medicine collects, analyses and integrates health-related data on an unprecedented scale. Electronic processing of such data (e:Med) plays a key role in such efforts. The programme will thus support development of international standards for data collection and compliance with such standards. Data provided by basic research and clinics will be suitably processed into useful and interpretable forms for researchers and doctors. For that reason, systems medicine funding projects will also be oriented towards enhancing the quality of cooperation between mathematicians and computer scientists on the one hand, with medical professionals and biologists, on the other.
In addition, methods and findings of biomedical basic research are to be applied to clinical practice. Systems-oriented approaches, such as sequencing of whole genomes, enhance the precision of diagnoses and the effectiveness of therapies. The e:Med programme will promote the growth of such expertise in clinical research environments, in a process involving initial validation steps with small groups of patients.

**e:Med: Moving towards systems medicine**

Systems medicine uses systems-oriented approaches, in both research and in clinical care, to illuminate complex physiological and pathological processes and, thereby, to create a basis for the development of innovative therapies and preventive measures.

The following section presents examples of the sorts of successes that are expected in the near term and in the medium-to-long term:

### Short-term successes (1-5 years)
- Practice-suitable formats for integration of data and models of different molecular and cellular levels
- Applications for routine use of individual sets of genetic and other "omics" data, for development of strategies in individualised medicine
- Rational models for prediction of synergistically functioning combinations of drugs
- Improvements in design of clinical studies, via modelling of side effects and consideration of genetic parameters

### Long-term successes (6-10 years)
- Prototypes of patient databases with integrated, functionally linked data
- Development of virtual disease simulating tools that can represent complex biological phenotypes
- Validation of model predictions, in animal models and in patients
- Development of software for individualised diagnosis and therapy

1.2.3 How e:Med is embedded within the Health Research Framework Programme

The e:Med research and funding concept is part of the Federal Government’s Health Research Framework Programme. Its primary objective is to enhance the quality and safety of health care by efficiently strengthening translational research. The Health Research Framework Programme is being implemented in six fields of action that are designed to enhance efforts with regard to different relevant research-policy challenges. The measures of the e:Med research and funding concept support the Federal Government’s Health Research Framework Programme in the area of application-oriented basic research in the life sciences and combine the programme’s other fields of action in a cross-sectional manner.

Systems-oriented medical research will provide new findings in a range of different areas:
- In research into multifactorially caused common diseases
- In prevention and nutrition research, in study of the complex interactions between pathophysiological processes and external factors
- In individualised medicine, via more comprehensive diagnostics and individually adapted therapy strategies

Such results will help enhance the quality of health care and will provide a basis for innovation in the health-care sector. Internationalisation of German research, via participation in major international research projects, and European-wide strategy processes, is another important strategic pillar of the endeavour.
2 Strategies and Measures

2.1 Strategies

The e:Med research and funding concept is applying the following strategies for establishing systems medicine:

2.1.1 Strengthening interdisciplinarity, pooling resources, building on funding policy successes

For effective collection, processing and use of life-sciences data, experts from the areas of basic medical research, clinical practice and information sciences have to cooperate synergistically. Interdisciplinary approaches, with horizontal knowledge transfer, can significantly facilitate application of findings, technologies and methods from basic medical research to clinical practice.

The e:Med concept especially promotes the sort of interdisciplinary cooperation that is indispensable for systems-oriented approaches in the medical sector. In the framework of its research funding, the BMBF plans to function as a catalyst for close cooperation between relevant stakeholders in the areas of clinical practice, basic medical research and information sciences. Experience has shown that new research fields tend to need support funding during their establishment phases. In the present context, such support will be provided through a proven approach: Promotion of effective, focussed research alliances that bring together all the expertise and resources needed to achieve a defined common objective.

Funding within the e:Med research and funding concept will be designed to build on and efficiently develop the innovation potential of existing funding priorities in the area of medical genome research and systems biology.

2.1.2 Strengthening application-oriented basic research

Major pharmaceutical companies have been scaling back their efforts in the area of disease-oriented basic research. Yet innovations for tomorrow’s medicine depend on successful basic research today. For that reason, the e:Med research and funding concept is designed to strengthen application-oriented basic medical research, as well as biotechnology companies’ participation in relevant research projects. It will pursue this orientation via attractive research objectives and “show cases” (cf. also section 2.2.2). In addition, it is set up to ensure that research projects take account, from the outset, of requirements – including the pertinent scientific frameworks, working conditions and resources – pertaining to implementation of research findings in clinical practice and in industry.

2.1.3 Promoting young scientists

Proper training and development of young scientists will necessarily play an important role in the process of establishing systems medicine as a research field. Young scientists must be part of the equation if the required interdisciplinary links between theoretical and application-oriented basic biomedical research and clinical research are to be built in any lasting way. To that end, specific, rapidly effective instruments for promoting young scientists and researchers are to be applied, such as funding of young scientist tandems and junior research groups (cf. also section 2.2.3).

2.1.4 Combining project funding with institutional funding

The e:Med programme joins state-of-the-art high-throughput technologies and information technologies via a cross-indicational, systems-oriented approach. The research and funding concept thus complements the efforts of the German Health Research Centres. The centres will be able to apply the findings emerging from the programme’s basic research to their own research, which is focussed on specific diseases, and cooperate with research groups being funded within the e:Med framework.

2.1.5 Promoting internationalisation

As a result of the scale on which it operates, systems-oriented medical research calls for international cooperation that can pool resources and generate “critical masses” of research capacities and personnel resources. What is more, pertinent binding international standards need to be established for collection, archiving and analysis of medical data. e:Med will create a strong national knowledge/resources base
and facilitate participation of German research groups in leading relevant international research initiatives. It will thus help enable the German research sector to achieve a leading international position. In the process, the e:Med research and funding programme will contribute significantly to “International cooperation in health research”, one of the fields of action of the Health Research Framework Programme.

2.2 Measures

The measures to establish systems medicine will be implemented in the framework of five modules. Suitable calls for proposals will be published for each module.

2.2.1 Module I: Systems medicine research consortia

Module I is the central measure within the e:Med research concept. This funding module has the objective of establishing systems medicine. Funding is aimed at setting up research consortia – interdisciplinary collaborative research alliances – oriented primarily towards testing of systematic, overarching research approaches not necessarily tied to specific diseases; advancing the area of effective data management, especially integration of different levels of knowledge; and enhancing networking between the health care and research sectors.

In the process, support will be provided for collaborative research alliances in which researchers from various theoretical fields (physics, mathematics and information science) and applied disciplines (life sciences and various clinical fields) can work together and develop a new culture of cooperation. The research work of such alliances has to relate clearly to disease. Research approaches interlinking several disease areas are expressly welcomed, but are not a fundamental requirement. To be eligible, a consortium must address a central research question that integrates all participating groups.

Instead of simply generating data, research should focus on functionally annotating data and integrating those within the meaning of systems medicine. The decisive factor in this regard is that data has to be analysed and modelled via information-science and mathematical methods. In this effort, systems medicine research approaches are expected to enhance our understanding of the complex structures of molecular networks, of how such networks are regulated and of how they function within pathophysiological processes. What is more, such research approaches are expected to provide new strategies for more precise – and, thus, more effective – therapies.

In addition, research consortia are also expected to advance the implementation of pertinent systems-oriented techniques, such as genome sequencing and proteome analysis, in clinical research. Research consortia will be free to test newly developed strategies for therapeutic interventions by carrying out initial tests with small groups of patients. The resulting findings will provide a basis for more precise – because more comprehensive – diagnostics, as well as for better targeted use of therapies, i.e. for individualisation of medicine. Finally, the obstacles to doctors’ use of such data are to be reduced.

2.2.2 Module II: Demonstrators for an individualised medicine

In this module, pilot projects will show how data from high-throughput research can directly enhance individualised prevention, diagnosis and therapy. Modern high-throughput techniques, along with advances in bioinformatics, now make it possible to collect and analyse ever-greater medically relevant data sets systematically, at reasonable costs. While the data sets involved carry enormous amounts of information, little research has been carried out to date regarding such data sets’ prognostic, diagnostic and therapeutic value in individualised medicine. Use of information sciences now needs to be intensified in making such data available for useful clinical application. For this reason, support will be provided for development of innovative methods and (bioinformatic) tools that can substantiate the direct benefits and applicability of systems-oriented approaches, drawing on data from high-throughput research, in individualised medicine. “Omics” data sets, such as genomic, transcriptomic, epigenomic and metabolomic data, along with correlating data, if relevant –
such as data on clinical phenotypes and environmental factors – are to be used to that end. Such work will emphasise ways of making data available, of usefully integrating and analysing data and/or of applying pertinent mathematical models. All cases must feature an outlook for clinical applications. Clinical testing on small groups of patients will be possible, subject to compliance with the necessary medical and ethical criteria. On the other hand, support will not be provided for clinical studies aimed at validations with large groups of patients. Module II is a suitable framework for support of research cooperation with biotechnology companies.

2.2.3 Module III: Young scientists

This module will provide a possibility for planned support of young scientists within the area of systems medicine. Such support will be oriented towards the following objectives:

- attracting outstanding medical professionals, computer scientists, mathematicians and biologists to this field
- strengthening cooperation between medical professionals, computer scientists, mathematicians and biologists, via support for horizontal knowledge transfer
- enhancing integration of computer science and mathematics in clinical training and research

Young scientists need to be given the opportunity to pursue their own research projects, independently, to build their scientific expertise and to establish themselves in the field of systems-oriented medical research. To that end, a range of existing barriers has to be eliminated, in the interest of fostering a lasting new culture of interdisciplinary cooperation. Module III will offer a range of different instruments aimed at early stages of careers.

Within the e:Med framework, Module III will function as a further-training module by supporting competitively equipped junior research groups (Nachwuchsgruppen; A), competitively equipped junior research alliances (Juniorverbünde; B) and (C) prominently staffed summer schools.

A) Junior research groups (Nachwuchsgruppen)

Module III A is aimed at German or foreign scientists with doctoral degrees or habitations. In each case, a project is to be applied for solely through the higher education institution or research institution at which the relevant junior research group is to be established. Consequently, young scientists who wish to apply for a junior research group have to reach relevant agreement in advance with a hosting higher education institution or research institution. Funding for junior research groups will provide for a group-director position, a postdoctoral fellow and up to two doctoral-candidate positions, along with customary levels of material and financial resources and travel allowances.

B) Junior research alliances (Juniorverbünde)

In a junior research alliance, at least three young scientists, whose doctoral degrees are not more than five years old, and who represent different fields, work together on a joint project. The framework for such project work, by the several partners involved in the junior research alliance, is contractually defined. Submitted research projects can include participation of biologists, clinical practitioners in various fields and theoretical scientists (mathematicians, computer scientists, physicists), although at least two of these categories must be represented.

Research alliances are expected to bring together the interdisciplinary expertise needed for achieving the relevant research objectives. The number of partners in each junior research alliance is determined by the research subject in question (at least three partners, but no more than five). Each research alliance project is represented by a coordinator. From the outset, junior research alliance projects have to be planned as interdisciplinary projects, and they must pursue systems-oriented approaches in medical research. Pertinent funding covers a position for the coordinator, along with customary levels of material and financial resources and travel allowances.
C) Summer schools

Three-day summer schools, staffed with leading scientists, give young medical professionals, biologists and mathematicians, in post-doc or medical-specialist training, the opportunity for concentrated, intensive further training in the area of systems medicine. Participation is restricted via a selection procedure. Participants incur no costs.

2.2.4 Module IV: Future-oriented and cross-cutting measures

This module is designed to cover systems medicine issues that are of great importance for key areas of systems medicine, and for the research field’s overall development, and that reflect the rapid advancements in this area and the innovation requirements and behaviour of relevant industrial sectors.

Research and funding measures designed with such issues in mind will become more and more important as the field advances; such a conceptual orientation provides the necessary basis for responding flexibly to the emergence of new research subjects and the intense worldwide competition for research findings and innovations in systems medicine.

2.2.5 Module V: Internationalisation

In the field of action “International cooperation in health research”, within the Federal Government’s Health Research Framework Programme, work is underway to enhance specialised cooperation with European and non-European research organisations and research-funding organisations. The important elements of this field of action include using synergies in the research policy sector, via actions such as harmonisation of strategic agendas and networking, and joint research funding.

In Germany, systems-oriented biomedical research is already on a high level. It achieves additional value added through close integration within the European and international research sectors. This module is designed to advance international networking in the German research sector, across a broad front. In the process, it seeks to take account of the diversity of international cooperation between funding agencies and research groups, and to work in parallel on a range of different relevant levels. The most important levels and measures include:

- Substantial participation in major international research projects, such as the International Cancer Genome Consortium (ICGC) and the International Human Epigenome Consortium (IHEC).
- (Leading) participation in a range of different European strategic research initiatives, such as the ERA-NETs and “Coordination and Support Actions” (CSAs) (CSA Personalised Medicine; ERA-NET for Synthetic Biology), and in measures for coordination and development of new fields (European Coordination and Support Action on Systems Medicine – CSA Systems Medicine).
- Joint concepts and calls for proposals in cooperation with European and international research funding agencies.
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