

Future Health

The Future of Health Care: deep data, smart sensors,
virtual patients and the Internet-of-Humans

Manifesto 2016

Further Information:

<https://ec.europa.eu/futurium/en/content/future-health-care-deep-data-smart-sensors-virtual-patients-and-internet-humans>



Every day European Union (EU) member states collectively spend more than €4 billion on health care

By 2025 more than 20% of Europeans will be 65 or older, with many in ill health and dependent on the work of others.



We are standing at an inflection point, with technological progress in a number of areas generating new ideas to solve one of the biggest challenges in our lives today – providing sustainable health care to a rapidly ageing population. The current challenge is harnessing this progress for the benefit of Europe’s 500 million citizens.

The **Future Health** Community* is asking the European Commission for support through a large-scale FET Flagship initiative to stimulate a paradigm change in health care by exploiting the most advanced **analytic, sensing, computing and communication technologies to enable personalised and preventative medicine in the framework of the Internet-of Humans.**

Support for **Future Health** will enable Europe to extend and increase its scientific excellence and competitiveness, driven forward by the creation of a cost-effective, sustainable, equitable and truly personalised pan- European health care system.

***The supporting parties of this Manifesto are listed in the Appendix**



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Section 1: Europe's inflection point

The Grand Challenge: Why do we need a Future Health flagship project?

Every day Europe spends more than 4 billion euros on its health care system¹, much of it on drugs, which help only a very small fraction of the patients receiving them², and the associated downstream costs of effectively untreated disease and unanticipated side effects³. Adverse drug effects kill more people than colon cancer, at enormous human and societal cost. This situation, already bad, is going to get worse: in an ageing society, fewer young people will have to take care of an increasing number of old and sick, and will have to finance rapidly increasing costs of health care⁴, threatening the stability of European societies. Our health care systems therefore not only need to deal with our increasing longevity, and the associated burden of chronic and degenerative diseases but also identify ways in which citizens stay healthy, active and productive for longer (also a current priority for the European Innovation Partnership on Active and Healthy Ageing⁵). The EU is calling for a long-term vision that will provide sustainability of health care systems through 'better spending' and initiatives that are capable of improving competitiveness as well as the quality of public services and peoples' quality of life.⁶

While we have been able to provide patients with individually optimal therapies in e.g. surgery, it has, up till now, not been possible to predict the effect and side effect of specific drugs on individual patients, since drugs, as molecular entities, act through complex interactions with enormously complex molecular networks, differing between individual patients. We have neither been able to characterise these networks in the individual patient, nor, even if we have had this information, to predict the outcome of this interaction for the individual patient. Patients therefore continue to be treated with drugs, which do not work, and/or do more harm than good. To change this, we will have to adopt a different strategy, which has been taken in all areas where we face complex situations - making mistakes, which are unavoidable in such complex situations, safely, cheaply and quickly on computer models of reality rather than in reality. Characterisation of these complex molecular processes and their interaction with e.g. the individual physiology of the patient can form the basis of 'virtual patient'/'virtual self' models of the individual allowing

¹ <http://ec.europa.eu/eurostat/web/health/health-care/data/database>;
https://en.wikipedia.org/wiki/Economy_of_the_European_Union;

² Nature vol 520, pg 610, April 2015

³ http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf; Bouvy, J.C., De Bruin, M.L. & Koopmanschap, M.A. Drug Saf (2015) 38: 437. doi:10.1007/s40264-015-0281-0

⁴ <http://bruegel.org/2016/01/innovation-and-sustainability-of-european-healthcare-systems/>

⁵ http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing

⁶ <https://ec.europa.eu/digital-agenda/en/news/communication-data-driven-economy>



systematic testing of all possible therapies or preventive (or wellness) measures, not on the real patient but on realistic computer models that are built and validated upon experimental big data collected by the most advanced technologies from molecular to macroscopic scales. For this, we will have to go far beyond the limits of what is feasible today based on new technologies to generate, new and advanced (spatially resolved or bulk) molecular, imaging and sensor data, new algorithms for their analysis and integration into models, new artificial intelligence (AI) and text-mining based approaches to extract information on mechanisms from the scientific literature to expand the basic model prototypes, which are then individualised based on the omics, imaging and sensor information available on the single patient. In tandem, the exploration of new computational and algorithmic principles to address the enormous computational challenges are required, alongside new principles in multiscale modelling uniting molecular, cellular and physiological mechanisms and data sources, as well as new mathematical, algorithmic and computation platform developments addressing the enormous problem of optimising parameter spaces of tens of thousands of dimensions based on very large pre-clinical and clinical data sets. Datasets that are generated from the most advanced sensing and energy efficient computing that created the Internet-of-Things (IoT) and, combined with data analytics, can transform it into an Internet-of-Humans (IoH).

We will have to generate more information on individual patients than we had about human biology a short time ago, based on detailed, ultimately spatially/single cell resolved molecular (genome, epigenome, transcriptome, proteome, metabolome etc.), clinical, imaging and sensor-based analysis techniques. We will have to generate predictive models exploring a wide range of different technologies, to integrate such enormous amounts of highly diverse, high quality information, generating integrated molecular, cellular, anatomical and physiological models, able to predict outcomes, optimised on preclinical and clinical data, and ultimately validated to the highest clinical standards by large scale clinical trials, not as a ‘moon-shot’ on a small number of individuals, but potentially on every patient in Europe, and ultimately the world, in a self-learning system; an IoH posing enormous computational and organisational problems, but offering unimaginable rewards in improving our health, in lowering the costs of vastly improved health care to society, and improving our personal freedom in dealing with our own biology.

Similar to the first landing of a man on the moon, this endeavour implies a massive, well-coordinated research and development program to make it overwhelmingly likely that all components required for revolutionary changes in the health care system will be available, when needed. A program supported through the standard measures of funding basic research is not enough. The costs for such a program, roughly one billion Euros over ten years, correspond to less than six hours of healthcare spending in Europe, many orders of magnitude below the efficiency gains expected in a system combining truly personalised therapy (and prevention)



choice, with the availability of new, lower cost drugs, triggered by the use of the same basic technology platform in extensive virtualisation of drug development.



Section 2: A real opportunity for Europe

A Game Changer

The *Future Health* community, a large, open and growing network from academia, industry and public office is proposing a 'game changer', - a vision of a truly individualised health care and disease prevention system in Europe based on a deep data (e.g. clinical, molecular, imaging and multi-scale sensor based) and computational modelling approaches to construct 'virtual patient-virtual self' models of dynamic nature. These models will enable doctors treating us for serious diseases to test and optimise their individual treatment strategy on a detailed computer model of our individual biology, but also help to guard against incompatibilities between us and the drugs we take, the foods we eat, and even the exercises we do (or don't do). In this vision, we will create the IoH, by a joint effort of medical and engineering communities; a seamless combination of technologies providing personalised health care services, capable of providing the best solutions for every individual person based on most advanced existing technology, computer models and vast amounts of data available from humans. The IoH will dramatically redefine the role of medical doctors, providing the most efficient error-free personalised treatments. Moreover, each patient will contribute with their own data to an increasing knowledge base within preventive health care.

This vision will trigger a paradigm change in health care, from oncology to many other disease areas (from neurodegeneration to metabolic disorders and ageing in general), as well as in prevention and in wellness applications, by exploiting and building upon current technological advances and innovations in Information and communications technology (ICT), molecular analyses, imaging and sensor techniques and computational modelling, together with new ways of exploiting big data to enable personalised and preventive medicine in the framework of the IoH. Approaches that will be intelligently combined to create the basis of a sustainable health care model and infrastructure, offering a new Quality of Life for the future of EU citizens.

Goals

Building upon existing European scientific excellence, capabilities and infrastructures, Future Health combines personalised/preventive medicine with IoT technologies to create a change of paradigm for a true revolution in sustainable healthcare in Europe. The paradigm change in health care will be also related to behavioural engineering and to sophisticated feedback loops for a healthy lifestyle, including complex interactions with the environment, taking into account the -omics and sensor information available on the individual. All these are expected to be the



basis for a future sustainable health care system, with a new Quality of Life that will be tested and implemented for the first time in Europe, with direct benefits to its citizens.

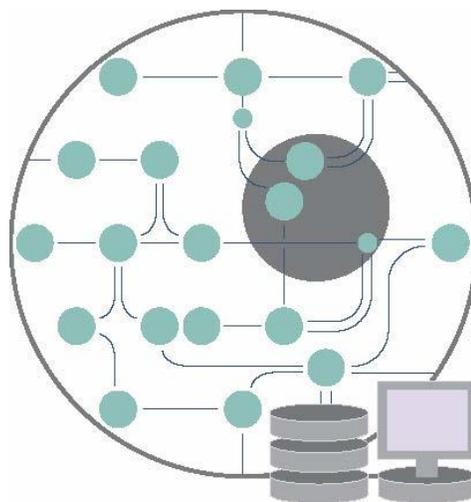
Future Health will:

- Directly address the enormous (and almost certainly irreducible) complexity of the biological differences between every patient and every disease through deep clinical, molecular and imaging analyses to be organized by algorithms and mathematical models.
- Provide a new generation of frictionless autonomous smart sensors at all levels required by health care data collection: implantable, wearable, environmental, providing clinical grade health monitoring in a hospital-without-walls setting. Develop new feedback-interfaces for life-style feedback loops and related diseases.
- Establish, optimise, validate and compare modelling systems based on different technologies (mechanistic, machine learning, hybrid) able to integrate all information available on every individual, optimised and validated through preclinical and clinical data (special clinical trials plus the continuous comparison of predictions and clinical results on the rapidly expanding set of patients analysed in this project).
- Develop computer models of every patient and disease state that allow physicians to test the consequences of all possible therapies/preventative and lifestyle measures in a virtual rather than the real patient, potentially guarding every European from before birth into old age.
- Acquire, store and redistribute the ever-accumulating amounts of data per patient required to fulfil this goal, within a strong governance framework, which protects personal data from misuse and ensures privacy and the full control of individuals over their own data.



Areas of Advanced Scientific Research and Development

- **Clinical/imaging/molecular survey techniques** (genome, epigenome, transcriptome, proteome, metabolome, immune status etc.) to provide a detailed characterisation of individuals in health and disease, for many of these techniques with ultimately single cell resolution.
- **New self-powered families of revolutionary sensors for IoH/truly personalised health care** based on **energy efficient approaches** and **heterogeneous integration** solutions in bio-compatible form factors to extend human senses and to support specific prevention strategies.
- **Self-learning mechanistic/machine learning models** translating this information into predictions on the future development of diseases (prevention) and the likely response to specific therapies and preventive measures, optimized and validated through preclinical and clinical studies.
- **Data security and availability:** hardware to software solutions specific for IoH/personalised medicine data. New human-machine interfaces for IoH/personalised medicine, personalised and capable of non-verbal interactions.



Roadmap

We have devised a 10-year-plan that has ambitious but practical goals, which will be addressed in a series of ‘working prototypes’ starting with oncology, until final rollout of a system ready to be implemented for multiple additional disease areas (e.g. rare diseases, metabolic syndrome/diabetes, heart disease, psychiatric diseases, neurodegeneration, ageing) on a large scale in European health care. The working prototypes will enable us to evaluate the life cycle feasibility of the approach, providing the opportunity to identify the specific barriers to adopting the Future Health strategy in terms of technology, regulations, acceptance (public and professional) and economic feasibility.

The Future Health roadmap will be outlined in detail during the preparatory action, but critical steps forward will be made through two projects that have support through the FLAG-ERA Joint Transnational Flagship Proof of Concept Call – *Information Technology: The Future of Cancer Treatment* (ITFoC) and *Frictionless Energy Efficient Convergent Wearables for Healthcare and Life Style Applications* (CONVERGENCE). ITFoC will provide the scope to demonstrate the feasibility of using a digital medicine and virtual patient modelling approach for Breast Cancer, developing and optimising key components, testing in the clinical environment and beginning the process of validating and quantifying the reliability of the approach, as well as the acceptability by users and payers. In tandem, CONVERGENCE will focus on developing smart autonomous sensor technologies and frictionless wearables to generate complementary data and will develop a quality assurance framework. It endeavours to exploit the potential of these new technologies for multi-parameter continuous monitoring in everyday life for true preventive medicine and a new Quality of Life and has the ambition to create and develop at European scale a diverse community and network of research partners to generate new research ideas and innovation. These two projects provide an opportunity to establish the road forward and provide proof-of-principle validation of the Future Health approach.

The effort is well balanced between: (i) deep -omics and imaging technologies, data analysis, (ii) smart and self-powered sensing technologies deployable at all-scales and capable of accounting for human health care interactions with the environment, (iii) energy efficient computing and communication techniques distributed locally and in-the cloud, capable of providing health care feedback in real time, with unrivalled latency⁷ (iv) big data analytics for IoH, (v) data integration, virtual patient models and (vi) personalised medicine validations and field trials.

⁷ <http://www.itu.int/en/ITU-T/techwatch/Pages/tactile-internet.aspx> (Extremely low latency in combination with high availability, reliability and security will define the character of the *Tactile Internet*. Tactile Internet, exploring its promise in application fields ranging from industry automation and transport systems to healthcare, education and gaming.)



Other initiatives to be developed and disease focus areas will be tailored according to the priorities of the individual member countries, through ongoing dialogues with, e.g. representatives of health care systems and ethical and regulatory institutions and the individual principle investigators from each country.

Future Health will be placed within the large and well-established framework of EU-funded projects and initiatives - past, present and future - within related domains, to highlight areas of synergy, co-operation and cohesiveness. Synergies with a range of ongoing European and global initiatives will be harnessed and new infrastructures created to enable the intelligent combination and exploitation of beyond state-of-the-art discoveries, through the research and development activities within Future Health, e.g.:

- **ICPerMed:** <http://www.permed2020.eu>
- **Lighthouse Initiative on Personalised Medicine - European Alliance for Personalised Medicine.**
- **Global Alliance for Genomics and Health (GA4GH):** <https://genomicsandhealth.org>
- **The International Cancer Genome Consortium:** <https://icgc.org/>
- **ICGCMED:** <https://icgcmmed.org/>
- **The 100,000 Genomes Project:** <https://www.genomicsengland.co.uk/the-100000-genomes-project/>
- **The Cancer Genome Atlas:** <http://cancergenome.nih.gov>
- **EIT Digital:** www.eitdigital.eu
- **EIT Health:** <https://eithealth.eu>
- **ECSEL:** <https://www.ecsel-ju.eu>
- **NEREID:** <https://www.nereid-h2020.eu>
- **BBMRI:** <http://bbmri-eric.eu>
- **EORTC:** <http://www.eortc.org>
- **Sysbio:** <http://www.sysbio.se>
- **ECRIN:** <http://www.ecrin.org>
- **PROPAG-AGEING:** <https://www.propag-ageing.eu/>
- **PhenoMeNal:** <http://phenomenal-h2020.eu>
- **CORBEL:** <http://www.corbel-project.eu>
- **EXCEMET:** <http://www.excemet.org/>
- **ELIXIR:** <https://www.elixir-europe.org/>
- **Italian Human Technopole 2040**
- **IRDiRC -** <http://www.irdirc.org>
- **IHEC:** <http://ihec-epigenomes.org/>



- **IMI2 Big Data for Better Outcomes (BD4BO) programme**

Currently there are four major phases planned:

Phase I: Initiation. Initial infrastructure development, development of improved pipelines for omics and imaging data integration in virtual patient models, implantable or wearable sensor solutions, pilot projects in oncology and life-style related diseases (e.g. Type II Diabetes). Selection of additional pre-pilots, based on submitted concepts (monogenic diseases, heart disease, psychiatric diseases, neurodegeneration, ageing). Establishment of the framework for model optimisation, testing and validation, including defining detailed specifications, testing and developing indicators of reliability. Model validation in preclinical experiments and specialised clinical trials. Establishment of a quality management system for all design stages.

Phase II: Expansion and Consolidation. Larger scale introduction of virtual patient models into routine practice in oncology. Development of successful pre-pilots into full-scale pilot projects. Development of virtual patient/virtual individual models for the vast majority of multi-factorial, non-infectious diseases, integrating -omics, imaging and sensor data.

Phase III: Maturation and Innovation penetration. Scale out and clinical engagement across Europe by full adoption of the new methods and innovation by technology-health care interactions, maintaining information feedback to further accelerate model improvement by clinical feedback systems. Expansion of the range of analytical data available on every patient through -omics and all-scale imaging and sensing technologies.

Phase IV: Full Implementation of paradigm shifts. Establishment and deployment in practicing health care systems. Effect and impact of personalised and preventive medicine quantifiable.



An example: Virtual Oncology

To establish 'virtual' oncology patients, we will use frozen tumor tissue and blood to generate detailed molecular analyses of both tumor and blood (minimally low coverage genome and deep exome of both tumour and blood, deep transcriptome of tumour) as a basis for personalising models of the tumour. Where possible, additional information will be generated (proteome/phosphoproteome data generated by both mass spectrometric and proximity ligation based analyses, tissue and serum metabolome data, spatially resolved transcriptome/proteome/metabolome analyses of tumor sections to analyse tumor heterogeneity, mutation and transcriptome analysis of circulating tumor cells, mutation and epigenome analyses of free tumor DNA from serum, deep immune status analyses from circulating B and T cells). Where possible, organoids/xenografts will be derived from fresh tumour material, to be used in a similarly deep molecular characterisation, but allowing as well, the analysis of drug response patterns to 100 or more drugs as well as detailed molecular analyses of time-dependent molecular changes during drug treatment.

Beyond the detailed (ideally spatially resolved) model of the tumour, the virtual patient models of oncology patients will take into account the individual pharmacogenomics of the patient based on the results of the genome/exome of the patient determined from the blood sample. Analysis that will be complemented by modelling of key tissues and cell types of the patient (to predict possible side effects of the drugs), as well as the immune system (to model immune reactions against the tumor, as well as the action of different immune therapies on the individual patient).

Models are originally established based on information in pathway databases and the scientific literature, e.g. in PyBios3 (<http://pybios.molgen.mpg.de>), an object oriented modelling environment, are updated, on a case-by-case basis, to incorporate additional variants, drug targets or pathways, based on AI/text mining techniques to be developed as part of this project.

After personalisation, object-oriented models automatically generate systems of differential equations, which can then be solved numerically. For this, we do however need values for the typically unknown parameters, which can be drawn from probability distributions. Therefore, major efforts will be focused on narrowing the range of parameter values in the parameter space, often with tens of thousands of dimensions. In this, we will have to overcome multiple challenges: the generation of the necessary data, the massive amount of computing power required for such parameter optimisation strategies, and ultimately the energy demand of any true personalisation of health care; challenges, which will be addressed at all possible levels (new hardware principles, new algorithms, parallelisation etc.).



Key Considerations

Can computer predictions really guide our health and wellbeing?

Predictions made by computer models already enhance and impact our everyday lives, from helping us to know what the weather will be like tomorrow to safety testing the cars we drive. Pilots are trained using computer models which allow them to make mistakes and crash ‘virtual planes’ until they are proficient enough to fly the real thing. This ‘risk avoidance’ strategy of using computer models for defining the optimal response in complex situations allows us to make unavoidable mistakes using computer models rather than in reality, ultimately improving designs, accelerating developments, reducing risks and cost and saving lives.

The enormous progress in technology and understanding of human biology in recent decades now makes it possible to apply a similar approach to human health and wellbeing. However, these major leaps forward have, as yet, reached neither our health care system nor the way we develop new drugs. Drug based therapy and prevention is still statistical, with many patients receiving drugs that are ineffective or, even worse, harmful. Unavoidable errors in drug development still cause the cost per drug reaching the market to remain in the multi-billion euro range and endanger patients participating in large, non-stratified clinical trials. In addition, our ‘health’ care system is still far too much a ‘disease’ care system. The majority of our efforts are focused on treating rather than preventing diseases; or at least diagnosing diseases (or their progression) early enough to be able to react. True personalisation of drug therapy and prevention, combined with extensive virtualisation of the drug development process can provide much better health (and where necessary, health care) at a fraction of the costs, with exponentially increasing efficiency, driven by the (exponential?) drop in cost of computing, sensors and –omics techniques, as well as the similarly exponential improvements expected in a system able to learn from its (over time increasingly rare) wrong predictions.

How reliable are the computer generated predictions?

Within Future Health, major effort is focused on developing a strong validation framework for improving the accuracy of predictions and generating indicators of reliability. Although current models are not perfect, they are in many cases - especially in oncology – already now likely to perform better than current clinical practice. As information on biological networks improves and disease mechanisms and parameters become increasingly well defined, based on a systematic comparison of predicted and actual therapy responses (in the case of drug treatments), overall accuracy will improve asymptotically. However, we need to be able to quantify this reliability. Steps forward in this direction have been made through a range of national and international



research projects and a validation framework is to be established within the FLAG-ERA project ITFoC, using breast cancer as proof of principle. This will entail the optimisation, validation and standardisation of the computational approaches used to predict drug responses based on as many omics and clinical data as currently obtainable. Benchmark tests will be conducted to further develop models and compare their performance in terms of sensitivity and specificity to determine the best simulation approaches. Models will be first validated in special clinical trials, but then, continuously, through the sanity check of comparing every prediction made with the clinical results, with the result of this comparison fed back to further improve the models (and our knowledge of human biology, disease and drug action mechanisms) in a continuing, ever expanding ‘model-vigilance’ system. This framework will enable the quantification of prediction accuracy through cross and independent cohort validation and subsequent generation of indicators of reliability, as well as a global drug response challenge, in which the wider community (including SMEs and industry) will be invited to test modelling methodologies within a joint platform.

Is this approach really feasible?

“All models are wrong, but some are useful”, N.R. Draper⁸.

The primary question is therefore not, if the predictions of a model are perfect, but if they are clearly better than existing alternatives, or at least can be made better with acceptable effort. Given the low response rates of many drugs, we are convinced, that (self-learning) models based on a detailed (clinical, molecular, imaging and sensor based) characterisation of every patient will, in many therapeutic areas, be able to quickly surpass the accuracy of alternative strategies. Costs will drop rapidly, not only driven through the rapid drop in costs of the driver technologies (computation, -omics, imaging, sensors), but also the learning effects observed in any large scale introduction of new technologies (e.g. solar cells in Germany). Widespread implementation will however pose additional (but solvable) challenges. With any change in paradigm come a variety of associated barriers to implementation. Evaluation requires analysis of ethical, regulatory, acceptance and economic issues, highlighting risks/benefits of the Future Health approach and setting in place a pathway towards the policy and regulations that will ultimately enable routine deployment of data- and model-based personalised therapy and prevention in Europe’s health care systems. Stakeholders (e.g. politicians, citizens, patient associations, health authorities, industry, ethicists, health economists, clinicians) will be consulted to address the difficult challenges of regulation, cost-effectiveness, public/clinician acceptance, and reimbursement in a

⁸ Box, G. E. P.; Draper, N. R. (1987), *Empirical Model-Building and Response Surfaces*, John Wiley & Sons. p424



diverse environment as Europe. This approach will rely on the sharing of information and the co-operation of researchers.

How safe will my data be?

All personal data will remain under full control of the individual, his/hers to share with physicians and, if they give permission, researchers. Feedback between predictions and treatment results, required to continuously improve the overall system, should, in our view, be automatic, to aid the continuous increase in the performance of the overall system, but highly protected to ensure the highest standards of data protection. Future Health is fully aligned with the concept of Health Data Cooperatives⁹ and the broad aims of empowering citizens through the implementation of data platforms for the safe storage, management and sharing of health-related data.

The data analytics will encompass the design of a specific infrastructure supporting both *local* and *in-the-cloud* data processing producing semantic information concerning specific health status and interaction with the environment. This will achieve unique features concerning on board integration of real time low level sensors data fusion, local integration of real time data visualisation, fog/cloud computing architecture with distributed early processing and on-cloud inception and integration of sensors nodes remote cross/re-calibration schemes, filtering, statistics computations. These require security and privacy issues beyond conventional web service frameworks by embedding security functionality with acquisition and compression at no extra energy cost.

Why do we need a FET-Flagship scale project?

Revolutionising healthcare in Europe will require a coordinated development effort on a very large scale, akin to the landing of the first men on the moon (and getting them back). In contrast to this enormous effort, which has now not been repeated for many decades, we aim to establish a new health care model ultimately improving and extending the lives of billions of humans worldwide.

Efforts on this scale cannot be performed as research projects, since they require a functional completeness. All essential components have to be developed within close specifications. Conversely, to save resources, redundancy, necessary to ensure success even if some particular developments fail, has to be limited (and planned). If John F. Kennedy had funded only a research program exploring ways to reach the moon at a similarly high level, we would still not be there.

⁹ Hafen E¹, Kossmann D, Brand A. Health data cooperatives - citizen empowerment. *Methods Inf Med.* 2014;53(2):82-6. doi: 10.3414/ME13-02-0051. Epub 2014 Feb 11.



If, instead of a planned and coordinated human genome project, we had continued to fund the sequencing of ‘interesting’ genes, we would, by now, have spent many times more than on the genome project, and would still not have the sequence of the genome completed.

A Flagship-scale project will provide:

- **Better healthcare at lower cost: Worldwide expenditure on health (≈10% of the world GDP on average), is at unsustainable levels,** (and still growing), strengthening the need for improved health care through truly personalised drug therapy, and improved prevention and early disease detection. Virtual patients (and virtual preclinical models) will revolutionise drug development; for example, virtual clinical trials prior to preclinical development, will streamline the drug development pipeline, providing more drugs more quickly, at much lower cost, and with much less risk. An approach that is aligned with EU and global calls for improvements in the competitiveness and quality of public services and people’s lives,¹⁰ the development of personalised medicine through the use of ‘-omics’ technologies¹¹, and strengthening of research and knowledge of personalised medicine¹².
- **The Internet-of-Humans, in itself a revolution,** in which the collection of big data enabled by most advanced smart sensing technology and the associated data analytics developed by medical experts, will serve, for the first time, personalised services in health care and experimentation on virtual patients for a sustainable error-free health care system. Moreover, the IoH will be capable of analysing the interactions of humans with the environment and life style and, beyond treatments, become a tool for behavioural engineering. Building the infrastructure and the concept of IoH (including advanced features of Tactile Internet) requires a FET Flagship for a duration of at least 10 years, with massive involvement of the whole European ecosystem.
- **The critical mass and competitive margin required to access and/or develop the most advanced technology and solutions for European health care systems.** Just like the landing of the first human on the moon, this is primarily a development project. We know much about what has to be done, but many concepts will have to be integrated into real systems, encountering and solving many challenges arising in any real, large scale application of theoretical concepts.

¹⁰ <https://ec.europa.eu/digital-agenda/en/news/communication-data-driven-economy>

¹¹ European Commission Staff Working Document on the use of ‘-omics’ technologies in the development of personalised medicine.

¹² World Health Organisation (WHO) 2013 Priority Medicines Report:
http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf



- **The required level of resources to enable rapid, large-scale diffusion of new solutions that will result in significant societal impacts.** Health is key to our existence and wellbeing, and therefore to everything else we are doing. This will generate a vibrant new economy, providing key resources to our continuing existence. A strategic FET Flagship involving IoT for health care has the advantage of balancing risk-taking academic research with pragmatic industrial approaches to enable the transformational effects of science and research at an early stage.
- **New technology that would allow efficient early detection of diseases.** By far, the most cost effective medicine is based on prevention/early detection. Virtual patients/in-silico self will revolutionise prevention strategies, by modelling the effects of preventive steps on the (artificial) ageing of the model.
- **Consolidation of European strength and leadership, especially in the domains of biggest impact, with high added economic value and opportunities for the creation of employment in many areas, such as the life sciences, pharmaceutical, health care, sensor and IT sectors.** For example, the ultra-low-power devices, sensors (functional materials, quantum effect based sensing, etc.), system architectures and wireless transmission (more than compression and duty cycling) are a central strength of Europe and key domains in a European collaboration between academia and European industry. These fields of the research act as enablers for the IoH and the future of health care.
- **Coordination at the broadest possible transnational level, enabling development of standards for privacy and security, jointly driven by technology and context.**
- **Security for mobile European citizens, through seamless data exchange and access to services throughout Europe** – a priority for health care data and technology-enabled approaches.
- **Creation of virtual patient/in-silico-self models,** accompanying every individual from before birth into old age, updated occasionally by deep molecular but also constant sensor information, will in the future protect individuals from dangers to their health and well-being, optimise prevention, aid in early detection of diseases, but also increase the range of possibilities for every individual to interact with their own biology.



Section 3: Impact & Benefits

Future Health Benefits

EU citizens, through a radical improvement of their health care and through a new quality of life, in which preventive medicine could induce a long-term paradigm change. Future Health will provide the technologies and the data required to help identify the right drug(s) for the right patient(s), through a data driven approach combining ‘virtual patient’ models with other techniques (statistics, machine learning) to predict, which available drug or drug combination would have the most positive impact on individual patients. The latter likely to be an important factor in improving adherence rates, a growing priority as prevention and care increasingly move beyond the confines of the hospital. This same set of technologies and the data generated would also help to accelerate the drug development process through virtualising major parts of the process. Large scale ‘virtual clinical trials’, comprising all patients (potentially millions) previously analysed in the ‘personalised medicine’ arm of the health care system, would provide a test-bed for new drugs. This would facilitate identification of patient groups most likely to respond to a new drug or drug combination, as well as potential biomarkers to identify sub-groups of responding patients in small, quick, and low-cost clinical trials, for rapid approval; however, as model-based therapy selection gains approval for routine clinical use, this inherently less powerful biomarker based selection of responders could be replaced by model-based therapy optimisation. Virtual trials also have the potential to reduce or even abolish the requirement for animal testing in pre-clinical drug developmental stages and ensure only patients who are most likely to respond positively to a drug will be enrolled in real-life clinical trials. Such a ‘pre-screening’ stage using virtual clinical trial technology is likely to become a future prerequisite for any clinical trial, helping to protect patient welfare and increase cost-efficiency.

European economy, through new job and employment opportunities. Formation of a new vibrant economic ecosystem bridging traditional engineering, computer sciences and health care, with unique opportunities for production in Europe. Reductions in sick leave and health related early retirement. Although difficult to quantify completely, we can expect long-term economic benefits many orders of magnitude higher than the anticipated costs of the proposed concept. Even a 1% saving of healthcare costs in Europe alone would, over a ten year period, generate savings of 140 billion euros.

Public finances, by curbing the uncontrolled increase in health care spending (potential savings of hundreds of billions of euros). Under our current model of personnel intensive, statistics driven health care, costs will inherently continue to rise in tandem with our ageing societies, leading sooner or later to some form of health care rationing. In contrast, data and computational model driven health care will continue to become more cost effective, driven by significant progress in computational and analytical techniques, and an exponentially increasing information base flowing back into an evolving, self-learning system.



European industry, including SMEs and covering a wide spectrum of fields from pharma to IoT. Exploitation of key technological advances and commercial opportunities for industries and catalyzation of a new European high-tech industry uniting health care and IT; in particular related to the goals of having, within Europe, the highly added value production facilities on smart sensors and smart systems, vital for the medical and automotive industries (as per the concepts of Smart Health, Smart Production, Smart Society proposed by ECSEL¹³ but taken in our flagship in a much longer term perspective and in an approach that is beyond the one of a bottom-up technology enabler). In this field we expect a strong emergence of startups and creation of a new ecosystem of industries with high innovation content, aiming at supporting new services for a Quality-of-Life in Europe. Industrial partners such as Bayer, Boehringer Ingelheim, Institut Roche, IBM, Siemens and Intel, are already strong supporters of the project.

Examples of industrial domains and expected benefits:

Internet of Things (IoT)

Leading industrial regions such as the USA and Asia are making substantial investments in the IoT, a field with a potential economic value of \$3.9 trillion to \$11.1 trillion a year by 2025 (equivalent to 11% of the world's economy)¹⁴. A comparable level of engagement within Europe is a priority. A strategic FET Flagship involving IoT for health care has the advantage of balancing risk-taking academic research with pragmatic industrial approaches to enable the transformational effects of science and research at an early stage. Future health will give a new dimension to IoT by developing the IoH, which will have unique features of security and privacy of medical data, access to personalised and preventive services and will embed technologies of Tactile Internet, creating new opportunities for the economy and creating new jobs at the European level.

Medical technology

Medical technology represents one of the biggest industries in health care, employing more than 570,000 people in Europe alone and with an estimated market value of €100 billion¹⁵. Future Health represents a source of new innovation and technologies to support this buoyant European market.

¹³ <http://www.ecsel-ju.eu/web/index.php>

¹⁴ <http://www.mckinsey.com/business-functions/digital-mckinsey/our-insights/the-internet-of-things-the-value-of-digitizing-the-physical-world>

¹⁵ The European Medical Technology industry: in figures. MedTech Europe 2015



Pharma

Only about one in 5000 drugs make it to market with considerable costs both financially and at the societal level. Drug development costs are becoming unsustainable; on average it costs \$2.558 million¹⁶ to develop and gain marketing approval for a new drug, with the consequence that fewer beneficial drugs are reaching doctors and patients with concomitant poor health outcomes. The technologies to be developed in this project will provide the technical basis to virtualise much of the drug development process. Virtual clinical trials with thousands and later even millions of (virtual) patients could, for example, in the future, already start before a drug candidate has been first synthesised. Preclinical experiments can be made much more informative by comparing predictions and results on the preclinical model, and then translating the result to the individual biology of the individual patient. The overall potential of these new developments could be enormous, reducing costs, reducing risks, reducing time, and generating orders of magnitude more approved drugs than before.

Potential applications: early drug development, supporting clinical trials of new drugs, drug repositioning, drug rescue, selection of optimal drug combinations, prediction of additive synergistic effects, reduction in animal testing in preclinical drug developmental stages.

Insurance companies

Just as in many other areas, insurance companies will benefit from improved health care at lower cost. Virtual patient/'in-silico self' models will however also benefit the industry by improving planning, since in the medium term the risk of specific events can be calculated, taking into account the detailed characterization of the insured individuals. This could also offer new possibilities to incentivize individuals to change aspects of their behavior, which increase their risk of disease.

Information and Communication Technology (ICT)

ICT forms the "threshold technology" of 21st century and is almost entirely built on a platform of electronic devices. Digital economies in highly industrialised nations increasingly depend on computing and communication with constantly decreasing cost and energy consumption. Indeed, applications built with advanced silicon CMOS technology are enabled by the aggressive scaling of the MOS transistor and the reduction of the cost per transistor by an amazing factor of 106 in only 35 years, a level never reached by any other modern technology. Indeed, ICTs play a

¹⁶ http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study



crucial role in boosting innovation, prosperity and competitiveness of all industry and service sectors.

In Future Health, the ICT field will be driven to novel horizons not solely by the enormous demand in computation power of the digital economy, but, in contrast to many other areas, by the energy efficiency and combination with other functions such as sensing and communication with high degree of data security and privacy, as required by health care. Such new demands will, in turn, drive ICT technology developments together with the required features of the IoH.

Nanoelectronics and smart micro/nano-systems

The domains of smart micro/nanosystems and of nanoelectronics are high on the strategic agenda of the European ICT research, and of crucial importance for leading European companies in the fields of health, communications, energy and automotive technology. Future Health will be an enabler of applications beyond the state-of-the-art in health care and IoH, paving the way for a high impact on the European economy.

The ultra-low power technology platform, encompassing sensing, computation, communication, harvesting and energy storage functions, will act as an innovation booster for European SMEs and start-ups. This will create concrete opportunities to keep and/or install new fabrication facilities in Europe, motivated by the high added value of the heterogeneous design and integration for smart systems for health care. The applications in preventive and personalised health care will extend at multiple levels of the semiconductor market, at all the levels of the semiconductor value chain, addressing both low-cost mass production and product of highly added value. The main applications in health and the ageing society, will extend and impact other sectors ranging from sports and well-being, to acute situation monitoring, rehabilitation, elderly monitoring, and, finally new tools for human behavioral engineering.

The project will make use of innovative (nano)technology and micro/nano sensing systems for interactive monitoring and assessment which falls under the definition of medical devices as per the European directive 2007/47/EC. An explicit aim of the project is to implement the technology and assess the potential for industrial manufacture and commercialization. As such, the European Union legal framework for medical devices will be taken into account. The project will strive to abide by the core legal framework which aims at guaranteeing a high level of protection of human health and safety. In particular, the European Union Medical Device Directive 93/42/EEC, and ultimately its ongoing revision which includes novel medical devices such as the one targeted will be taken into consideration.





Appendix:

Collaborators and Support

The idea and the related goals of this proposal find support in previous FET Flagship initiatives: 'ITFoM: IT Future of Medicine', led by Prof. Hans Lehrach (Max Planck Institute for Molecular Genetics, Berlin), and 'Guardian Angels for Smarter Life', led by Prof. Adrian Ionescu (Ecole Polytechnique Fédérale de Lausanne). The technological roadmaps and the networks of partners generated by these two pilot flagship projects create a unique opportunity for implementing a joint concept proposed here. In this way partners from medicine, science and engineering, industry, finance, health care funders, patient organisations, regulators, administrators and the general public will join to develop a stepwise, global, coherent and integrated path towards truly personalised medicine and prevention in Europe (and beyond).

Future Health is open to new supporters and partners

The proposal is strongly supported by a (growing) large network of universities, research institutes, industries and individual leaders, including:

- **Aarhus University, Denmark:** Lars Bolund, Professor
- **Acabidem University, Turkey:** Ugur Sezermen, Professor
- **Alacris Theranostics, Germany:** Bodo Lange, CEO
- **Bayer HealthCare, Germany:** Andreas Busch, Head of Global Drug Discovery, Member Executive Committee
- **Berlin Institute of Health (BIH), Germany:** Erwin Böttinger, CEO, Professor
- **Catalan Institute of Nanoscience and Nanotechnology, Spain:** Clivia M. Sotomayor Torres, ICREA Research Professor
- **CEA DRF, France:** Nora Benhabiles, Director, External Collaborations and Industrial Research. François Sigaux, Professor, Executive Scientific Director of Basic Research.
- **CEA/DRF/IG/CNG, France:** Jean-François Deleuze, Director
- **CEA/DRT/LETI, France:** Marie-Noelle Semeria, Director; Thomas Ernst, Chief Scientist
- **Centre of Innovation in Medicine, Romania:** Marius Geanta, co-founder
- **Charité, University Medicine Berlin, Germany:** Antonia Jousen, Professor of Ophthalmology. Chair, Department of Ophthalmology; Peter Hufnagl, Professor, Institute for Pathology, Leader Digital Pathology; Plamen Simeonov.
- **CIRMMP (Consorzio Interuniversitario Risonanze Magnetiche di Metallo Proteine), Italy:** Claudio Luchinat, Professor of Chemistry.



- **CNAG-CRG (Centro Nacional de Análisis Genómico), Spain:** Ivo Gut, Professor, Director
- **CNIA (Centro Nacional de Investigaciones Oncológicas (CNIO), Spain:** Alfonso Valencia, Professor, Group Leader
- **Estonian Genome Centre, University of Tartu, Estonia:** Andres Metspalu, Professor, Director
- **ETH Zürich, Switzerland:** Christofer Hierold, Professor, Chair in Micro and Nanosystems, Lothar Thiele, Professor, Chair Computer Engineering and Networks; Rudi Aebersold, Institute Molecular Systems Biology
- **European Alliance for Personalised Medicine, Belgium:** Denis Horgan, Executive Director; David Byrne, Co-chair
- **Fraunhofer Research Institution for Microsystems and Solid State Technologies, Germany:** Peter Ramm, Head of Department, Heterogeneous System Integration
- **Fraunhofer Institute for Algorithms and Scientific Computing (SCAI):** Martin Hofmann-Apitius, Professor, Head of Department, Bioinformatics
- **Fraunhofer ENS, Institute for Electronic Nanosystems:** Thomas Otto, Professor, Director
- **Grenoble Institute of Technology, France:** Francis Balestra, Vice-President
- **Harvard Medical School, USA:** George Church, Professor of Genetics, Director of PersonalGenomes.org
- **Helmholtz Centre Munich, Germany:** Jan Hasenauer, Group Leader German Research Center for Environmental Health
- **IBM Zurich, Switzerland:** Heike Riel, Director Physical Sciences IBM
- **Institute Roche:** Patrice Deneffe, Director
- **IMEC, Leuven, Belgium and IMEC-NL, Eindhoven, the Netherlands:** Chris Van Hoof, Program Director Wearable Healthcare, Professor KU Leuven, Leuven, Belgium
- **IMT (National Institute for R&D in Microtechnologies), Romania:** Raluca Müller, CEO, President of the Board
- **Infineon Technologies AG Munich, Germany:** Knut Hufeld, Director, Research & Development Funding, Infineon Technologies AG; Reinhard Pufall, Dr
- **INSERM, France:** Georges Dagher, Infrastructure Biobanques, Director
- **Institut ROCHE, France:** Patrice Deneffe, Head of Institute
- **Institute of Electron Technology (ITE), Poland:** Piotr Grabiec, Professor, Head of Division
- **Intel Corporation, Ireland:** Charlie Sheridan, Director, Internet of Things (IoT) research Lab at Intel Corporation
- **Kings College London, UK:** Tony Ng, Richard Dimbleby Professor of Cancer Research, King's College London and Professor of Molecular Oncology at UCL-Cancer Institute,



University College London; Tim Hubbard, Professor of Bioinformatics, Head of Bioinformatics at Genomics England and Honorary Faculty at the Wellcome Trust Sanger Institute in Cambridge, UK

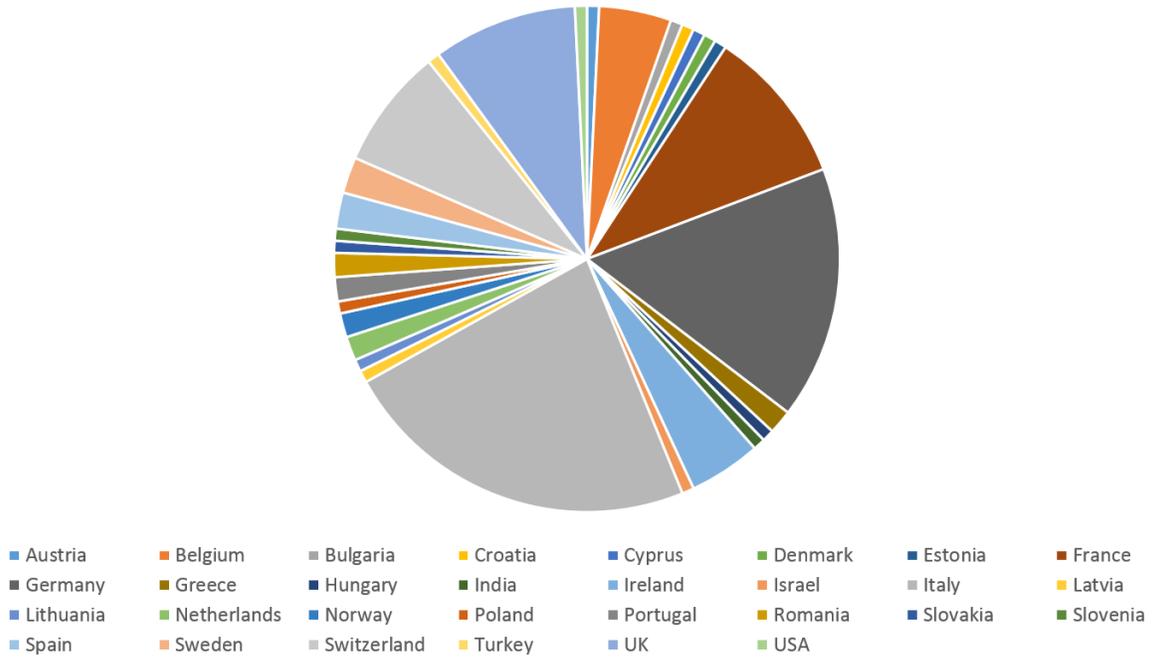
- **KTH, Royal Institute of Technology, Sweden:** Mikael Östling, Professor
- **Max Planck Institute for Biology of Ageing, Germany:** Adam Antebi, Professor, Director
- **Max Planck Institute for Colloids and Interfaces, Germany:** Peter Seeberger, Professor, Director
- **Max Planck Institute for Heart and Lung Research, Germany:** Thomas Braun, Professor, Director
- **Max Planck Institute for Infection Biology, Germany:** Thomas Meyer, Professor, Director
- **Max Planck Institute for Molecular Genetics, Germany:** Hans Lehrach, Professor, Director Emeritus; Alexander Meisner, Director; Bernhard G. Herrmann, Professor, Director; Marie-Laure Yaspo, Group Leader
- **Max Planck Institute for Molecular Cell Biology and Genetics, Germany:** Gene Myers, Professor, Director
- **Max Planck Institute of Microstructure Physics, Germany:** Stuart Parkin, Professor, Director
- **Max Planck Institute of Psychiatry, Germany:** Elisabeth Binder, Director
- **Maastricht University, Netherlands:** Angela Brand, Founding Director, Professor, Institute for Public Health Genomics (IPHG)
- **Manipal University, India:** K Satyamoorthy, Director/Senior Scientist/Professor and Head of the Division of Biotechnology, Centre for Molecular and Cellular Biology at School of Life Sciences.
- **Medical University Graz, Austria:** Kurt Zatloukal, Professor of Pathology
- **Oslo University Hospital, Norway:** Eivind Hovig, Head of Bioinformatics
- **Riga Stradins University, Latvia:** Edvīns Miklaševičs, Professor, Director, Institute of Oncology
- **Science for Life Laboratory, Sweden:** Olli Kallioniemi, Director
- **Siemens AG, Germany:** Max Fleischer, Professor, Cord Friedrich Staehler, Healthcare CTO
- **Sinano Institute and IMEP-Grenoble INP - IMEP-Grenoble, France:** Francis Balestra, Director of Research NRS
- **SINTEF, Norway:** Maaike M Visser Taklo, Chief Scientist
- **Slovak Academy of Sciences, Institute of Molecular Biology, Slovakia:** Jozef Simuth, Professor



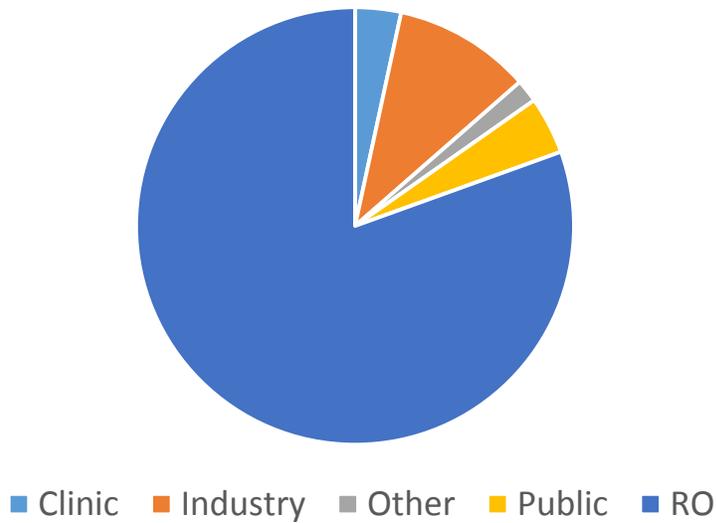
- **Stephan Angeloff Institute of Microbiology at the Bulgarian Academy of Sciences, Bulgaria:** Hristo Najdenski, Professor, Director
- **Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland:** Adrian Ionescu, Professor
- **SYSBIO (Centre of Systems Biology), Italy:** Lilia Alberghina, Professor, Director
- **Tel Aviv University, Israel:** Ron Shamir, Raymond and Beverly Sackler Professor of Bioinformatics
- **Tyndall National Institute, Ireland:** Alan Mathewson, Deputy Head-Circuits and Systems; Kieran Drain, CEO of Tyndall National Institute
- **UCL Institute of Neurology, UK:** Xavier Golay, Professor, MR Neurophysics and Translational Neuroscience Head, Department of Brain Repair and Rehabilitation
- **University of Bologna, Italy:** Enrico Sangiorgi, Vice Rector, Professor, Giorgio Baccaranni, Professor, Luca Selmi, Professor
- **University of Cambridge, UK:** John Robertson, Professor of Electronic Engineering
- **University College Dublin, Ireland:** Walter Kolch, Professor, Director of Systems Biology Ireland
- **University College London, UK:** Stefan Beck, Professor of Medical Genomics; Ann Blandford, Professor of Human-Computer Interaction & Director of UCL Institute of Digital Health, UCLIC & Department of Computer Science University College London, UK
- **University of Copenhagen, Denmark:** Søren Brunak, Professor, Research director, Novo Nordisk Foundation Center for Protein Research
- **University of Lisbon, Portugal:** João Lacerda, Professor, Group Leader
- **University Medical Center Göttingen, Germany:** Heyo Kroemer, Professor, Chairman of the Managing Board of the University Medical Center Göttingen. Dean of the Faculty of Medicine, Georg-August-Universität Göttingen
- **University of Milano-Bicocca, Italy:** Marialuisa Lavitrano Professor of Pathology and Immunology
- **Université catholique de Louvain, Belgium:** Denis Flandre, Professor; Jean-Didier Legat, Professor, President of the ICTEAM institute; Benoit Macq, Professor; David Bol, Professor; Laurent Francis, Professor
- **Uppsala University, Sweden:** Ulf Landegren, Professor
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Countries



Organisation Type



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