BETTER RESEARCH FOR BETTER HEALTH

A vision for health and biomedical research from the Scientific Panel for Health*

Biomedical and health research are drivers for better health and patient care through innovation and implementation into practice of novel findings. In a changing society new challenges demand a new research and innovation framework and strategy.

*The European Commission's Scientific Panel for Health (SPH) is a science-led expert group based on the provisions of the Horizon 2020 Specific Programme that has been tasked with helping to achieve better health and wellbeing for all.
https://ec.europa.eu/programmes/horizon2020/en/h2020-section/scientific-panel-health-sph

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EXECUTIVE SUMMARY

The value of health and biomedical research

Improved health and wellbeing of the people is the ultimate goal of research. This societal aspect is an important and traditional characteristic of European1 research and its emphasis and orientation toward humanitarian goals and solidarity. In addition, health contributes to economic prosperity. Research underpins every step in the innovation cycle, from discovery in bench and bedside research, to implementation in healthcare, and prevention. It is part of a vision of science and knowledge in a participative society.

Health and research policies must support these values when addressing present challenges and opportunities.

Challenges, opportunities and strengths

Health and disease are global and are intricately linked with health in animals, plants and agriculture. Any research and action plan must include a European- and world-wide dialogue.

Diversity in a multi-generational population will require age-specific approaches. Taking a lifecycle approach, with an increased focus on child health may offer opportunities to address acquired life-style related disease. Major medical challenges include mental health and degenerative disease.

A new approach to health and disease based on causative pathways that include genes, environment and life-style generates 'Big Data' for individuals. This creates potential for pre-emptive and improved preventative approaches targeting health, and tailored treatments aiming for precision medicine with treatment according to aetiology. Research must explore the feasibility and affordability of the expectations created by these opportunities.

Patients', and society's, engagement with health research contribute to the rich collection of population cohorts and biobanks in Europe, and to high quality clinical research. Organised healthcare systems in Europe support clinical, prospective and outcome studies, and can generate 'Big Data' at population level. They further unlock the potential of Digital Health.

The integrated use of Information and Communication Technology (ICT) for the design, support and networking of all data requires all participants in European healthcare. It aims at higher health literacy of Europe's citizens, improving diagnosis and treatment, and enhancing economic productivity in traditional and in new health markets.

'Big Data' and fast innovation through smart and 'disruptive' technologies, require new models for research and a next generation of highly qualified researchers, working in multidisciplinary networks. An adaptive legal and ethical framework is needed to facilitate this research, to support data flow, and to ensure the safe development of "unexpected" discoveries without hindering implementation.

How to advance and boost health research

- facilitate high quality cross-border collaboration within Europe and beyond
- nurture multi-stakeholder research across the innovation cycle and find common goals
- integrate and assess the potential of novel and disruptive technologies
- ensure a comprehensive and aligned, facilitating regulatory framework
- involve citizens and patients
- create value, through health, and a knowledge-based society

A call for action

Preventing disease, prolonging life and promoting health is best achieved through the integrated and organized efforts of research and society at all levels. This requires not only national action, but intensified cooperation at European and global levels.

Cross-border research, cross-border consultation and comprehensive policies are required. EU programmes have demonstrated the power of collaboration inside and outside of Europe, but much more is needed, both within the EU institutions[2] and beyond. EU institutions can lead by example in addressing the dispersion of policies across different authorities and administrations, and providing an integrated regulatory and ethical framework facilitating health research and innovation.

Implementation of a comprehensive policy will require action across sectors, and the involvement of the whole of society. "Health-in-all policies" has to become a priority in science, in the private sector, in politics and public bodies, and in civil society and should become a landmark for research in Europe. Public engagement in the health debate must increase. Citizens should be actively involved in health and research policies, and new ways for citizens to access health information and services should be developed.

Setting priorities requires a balance between addressing medical needs and building on opportunities, and must ensure excellence. A comprehensive research policy needs scientific leadership, continuity and broad consultation at a scale that takes full advantage of the European Research Area.

To make a real difference at the global scale, a more proactive policy and international commitment of Europe in this area is urgent. EU programmes should be coordinated with the national priorities of national governments in Europe to make a real difference at the global scale. Europe, its Member States and EU institutions, need a comprehensive vision, setting out a joint strategy and action plan in consultation with all stakeholders.

The EU and Member States hold a unique position to further investigate the concept of a science-led European Health Research Council, Institute or platform[3]. It could develop and support a global vision and research policy within the European context, and boost excellent research through enhanced cross-border collaboration, building on the success and potential in Europe.

The Scientific Panel for Health[4] is a pilot of such an approach, but a dedicated body for European Health Research is needed for a long term commitment to better research for better health in Europe.

Better research for better health needs

- a comprehensive policy for health research, defining common actions across EU and member states, including all actors

- implementation of 'health in all policies'

- a long-term mechanism to ensure the best strategies and highest quality in health research by a science-led multi-stakeholders' platform, including patients and society at large

1. THE SCIENTIFIC PANEL FOR HEALTH

The Scientific Panel for Health (SPH) was created under Horizon 2020, in response to concerns from a broad community of stakeholders in biomedical & health research, professionals in health care, biotech and industry, and patients[4]. Changing health and disease presentation (chronic diseases, infectious diseases, mental disorders and an aging population) is expected to decrease the labour force and raise healthcare costs. In relation to research and its implementation, there is concern about the loss of competitiveness in Europe and a reduced drive towards innovation. Efforts have to be made at the European level because of the transnational dimension of research, with distributed expertise and human resources, infrastructure, and the need to reach critical mass. A European initiative would allow such out-reach beyond Europe. To address these concerns, strong input from the scientific and stakeholders community is needed.

Members of the SPH were appointed by DG Research & Innovation in December 2014, with work starting in January 2015. More information on the outcomes achieved thus far is available on the SPH web-page[5].

The SPH has complementary objectives: on the one hand to provide a comprehensive, long-term vision for research and innovation, and on the other hand to identify concrete challenges and propose solutions for the hurdles and barriers to innovation. Consultation and interaction with stakeholders is integral to the work of the SPH.

Three working groups were initiated and are ongoing:

- The first working group addresses hurdles in translation, in making new interventions available to patients, and in implementation of new treatments into clinical practice.
- The second working group focuses on a long-term strategic research agenda. Priorities for development should marry unmet clinical and societal needs, to opportunities and strengths. The development of such a long-term agenda includes reflection on the process and broad consultation.
- The third working group investigates the needs of the new workforce required for research, from ideas to implementation. Novel competences currently not in the training packages need to be expanded, such as the use of Big Data, the regulatory environment and the ethical framework. Entrepreneurship needs to be developed and novel career paths fostered. The SPH working groups will include the broader community of scientists and stakeholders through consultation on these themes.

The specific work however, needs to be positioned within a wider comprehensive review and analysis, with an overarching long-term view for policy and strategy. The present document provides an overview of challenges and opportunities, and of the strengths of Europe, and sets out the vision of the SPH for a way forward. It was developed as a working document in 2015, and was updated based on consultation and discussion with experts and participants at the first SPH conference held on January 21, 2016 in Brussels[6].

2. THE VALUE OF HEALTH AND BIOMEDICAL RESEARCH IN AND FOR EUROPE

2.1. Health is a societal value - the European vision for mankind

Europe views health as a fundamental human right, accessible to all. Health care is a public and societal responsibility, where patients are viewed as people, not as clients of corporations. This vision is rooted in a long history developing the concepts of freedom and human rights.

Achievements in health care have enhanced life expectancy and quality of life: people with rare diseases, chronic disease and disability are not a burden but full members of a society rich in diversity. Health is not just the absence of disease, but about an individual's ability to lead a self-determined, autonomous life. The availability of comprehensive, reliable and individualized health information, will allow (and encourage) individuals to participate in decisions about their health.

The World Health Organisation (WHO)'s 1946 Constitution defines good health not just as the absence of disease or infirmity but as "a state of complete physical, social and mental wellbeing"[7]. Health is not simply about living, but is a resource for life; it is a "positive concept emphasizing social and personal resources as well as physical capabilities". The Constitution further states that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition", an idea also highlighted in the Universal Declaration of Human Rights of 1948.

This concept is well accepted by the EU, as reflected in the EU's Charter of Fundamental Rights (article 35) which states that "everyone has the right of access to preventative health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities"[8]. The idea of healthcare as a basic responsibility of the state sets the EU apart from the US' more market-driven approach to healthcare. For example, in 2010, 50% of US healthcare funding came from private funds, compared to 38% from federal funds and 12% state and local funds, with most healthcare delivered privately, even if publicly financed[9].

As well as being a fundamental human right, health, and a healthy population is valuable to society. Advancements in health care now mean that individuals with rare diseases, chronic diseases and disability are more able to live active, healthy and long lives. Far from being a burden, they can contribute significant benefits to society and should be viewed as full members of a population. For example, a 2011 study by the Royal Voluntary Service[10] concluded that in 2010, despite the costs of providing health services, welfare and pensions, over 65s made a net contribution of £40 billion to the economy through taxation, spending power, the provision of social care and the value of their volunteering, and it is predicted that their net economic contribution will grow to £77 billion by 2030[11].

2.2. Research brings health and benefits to society

Achievements in health have been driven by research and innovation and by the high value placed on science in a free and open spirit of (self) critical thinking.

Research in the humanities, natural sciences and technology are one with health and biomedical research, in a holistic view of humankind.

Scientific integrity is part of a broad ethical framework where science is embedded in, and at the service of, society.

Education and science are the basis of the future knowledge society, for discovery and innovation, and a participative society. Europe has invested in education and research institutes that foster these values.

The value of open and interdisciplinary science in Europe was highlighted as early as 1834, by Mary Somerville in her book "on the Connexion of the Physical Sciences", when she wrote:

"The progress of modern science has been remarkable for a tendency to simplify the laws of nature and to unite detached branches by general principles[12]".

Science Europe, an association of European Research Funding Organisations (RFO) and Research Performing Organisations (RPO), based in Brussels, further emphasises the importance of collaborative, interdisciplinary working as key underpinning values in European science, arguing that "cooperation in research leads to critical mass, European added value and ultimately better science with higher impact" and that "a key to future scientific breakthroughs lies in interdisciplinary research". They also emphasise the importance of open science, stating that "all research and innovation builds on the capacity of scientists, research institutions, businesses and citizens to openly access, share and use scientific information"[13].

These values were most recently reflected in Carlos Moedas' (Commissioner for Research, Science and Innovation) 2015 speech, entitled 'Open Innovation, Open Science, Open to the World', which lays out a framework for the future of scientific research in Europe[14].

Many influential stakeholders across Europe[15], including the European Research Council and the European Science Foundation (ESF) (the functions of which have now been transferred to Science Europe) place high value and importance on biomedical research. Europe has a responsibility to develop new scientific advancements, with Eugen Seibold, the 1990 ESF President stating that:

"Modern science was born in Western Europe. Therefore, as Europeans, we have a special responsibility for the further development of this child"[16].

Jose Mariano Gago, CERN researcher and Portugal's Minister of Science and Technology for seven years, further emphasized that science and scientific integrity must be embedded in, and at the service of society, advocating for science to become an integral part of culture. He argued that:

"The sharing of knowledge is quite simply a question of democracy, and even of justice"[17].

The European Science Foundation states that "biomedical research has had a major impact on European citizens and society" and "for the future, biomedical research holds more promises". The Alliance for Biomedical Research in Europe also states that, "research is the key to identifying causes of disease and developing strategies for health promotion and prevention, as well as diagnosis and treatment"[18.]

The ESF specifically highlights a number of impacts biomedical research has had on society over the last 40 years, including:

- *significant reductions in infant mortality through social and public health advances, including immunization;*
- *the development of efficient drugs to drastically improve the treatment of heart attacks, high blood pressure, schizophrenia, and most recently, AIDS and cancer;*
- *technical advancements such as ultrasound and MRI scanning leading to much more accurate diagnosis of disease, and better treatment pathways;*
- *major improvements in surgical and anaesthetic techniques; and*
- *improved access to artificial joints and organ transplants[19].*

2.3. Biomedical and health research bring economic value

Research and innovation have advanced medical diagnostics, therapeutics and technology in many fields, with major impact on both life expectancy, and healthy life years (HLY). Society gains economically from these additional years of good health and productivity. Innovation in biomedical and health research can create new companies and jobs, boosting the economy.

As well as health and social benefits, biomedical research has great economic value: it boosts competitiveness and innovative capacity, facilitating economic growth[20]. More generally, a healthy population can act as "an essential component of development, vital to a nation's economic growth and internal stability"[21] and it is now acknowledged that improvements in health play a vital role in reducing poverty. For example, according to the OECD[22], a 10% improvement in life expectancy is associated with a rise in economic growth of some 0.3-0.4 percentage points a year.

Two recent (2008, 2014) studies in the UK conducted by RAND[23], highlight the significant economic return on investment in biomedical research. For each pound invested by the taxpayer in the UK to support cardiovascular disease, mental health research and cancer, the benefits produced equate to earning 39 pence, 37 pence and 40 pence respectively, each year 'in perpetuity'. A 2011 study by Batelle[24] also highlights the significant returns in investment that biomedical research has had. The US Government invested $3.8 billion in the Human Genome Project between 1988 and 2003 and between 1988 and 2010, this investment had a total economic impact (direct and indirect) of $796 billion, created 3.8 million job-years of employment (310,000 jobs in 2010), with a total personal income of over $244 billion. In other words, for every $1 invested, $141 was generated in the economy.

Health and research policies must support these values when addressing present challenges and opportunities.

3. CHALLENGES AND OPPORTUNITIES

3.1. Health and disease are global

Both infectious and non-infectious disease are globally patterned. Infectious disease's global spread is related to increased mobility, both in the short-term and long-term, and to short and long-distance migrations. Changes in lifestyle, demographics and environment are leading to changing patterns of non-infectious disease globally.

Human health and disease are intricately linked with health in animals, plants and agriculture, requiring a 'One Health' approach.

Digital Healthcare approaches enable delivery of high quality care by exporting and leveraging EU-developed solutions, such as telemedicine in Africa and Asia.

Globalisation and the movement of people between regions, countries and continents means that health and disease must now be considered on a global scale. The movement of people leads not only to the global spread of isolated infectious diseases, but also the spread of cultures, values and lifestyles which influence the prevalence of non-communicable diseases (NCDs) such as diabetes and obesity.

Infectious diseases can be separated into four main categories: Poverty-related diseases (PRD) including HIV/AIDS, malaria, tuberculosis and hepatitis; Anti-microbial drug resistance (AMDR); Emerging Epidemics (EE); and Neglected Infectious Diseases (NID) e.g. rabies and leprosy. The European Commission's (2013) document on Improving health for all EU citizens[25] highlights HIV/AIDS as a key health issue in the EU and worldwide, along with cross-border health threats including the H1N1 influenza pandemic in 2009, the 2011 E. Coli outbreak, and the 2015 Ebola outbreak. They also identified the potential side effect of infectious disease spread - antimicrobial resistance - as a major issue to address. Anti-microbial resistance is estimated to be the cause of 25,000 deaths per year and lead to an additional EUR 1.5 billion in healthcare costs and productivity loss[26].

The international spread of non-communicable diseases is also an important concern. Of the 57 million deaths occurring in 2008, 36 million (63%) were due to NCDs, mainly cardiovascular diseases, diabetes, chronic respiratory disease and cancer. The large majority of these (80% or 29 million) occurred in low and middle income countries. The WHO predicts that the number of NCD deaths will increase by 15% globally between 2010 and 2020 (to 44 million deaths). In Europe, there is predicted to be no increase, while in Africa, South-East Asia and the Eastern Mediterranean they are predicted to increase by over 20%[27]. This highlights the need to engage in a worldwide dialogue and take an international approach to NCDs.

However, diseases do not just spread from person to person, they can be transmitted from plants and animals. In fact, approximately 75% of new emerging human infections originate from zoonotic agents, meaning they are transmitted from animals to humans. This includes some of the most recent and widespread human disease epidemics such as Ebola, HIV, dengue and MERS CoV. Furthermore, it is now clear that changes in the environment due to population growth and climate change are drivers for the emergence of these zoonoses[28] meaning that it is vital for disease and disease spread to be considered in a much wider, ecological context.

The One Health Platform[29], a strategic forum of stakeholders and a reference network, is already trying to work within this wider context. It aims to promote the idea of an intrinsically linked system of disease and develop a better understanding of the ecological and environmental factors that impact on human disease, through promoting an integrated approach to research. Their overall aim is to improve our preparedness for the current and future outbreaks of zoonoses, emerging infectious diseases in both plants and animals, and antimicrobial resistance.

Many articles mention the potential of telehealth as a global solution to the interconnected nature of disease, and as a way of improving access to care for individuals in rural and remote locations in the developing world[30]. Currently, common clinical applications include teleconsultation, telecardiology (the transmission of ECGs), teleradiology, and teledermatology, although the application of mobile solutions (m-health) is also on the rise. However, while many telehealth programmes exist through Latin America and the Caribbean, Asia and Africa, there is not much published evidence or examples of sustained usage.

There is an obvious need for the expansion of such technologies. For example, Africa is home to 14% of the world's population and struggles with 24% of the global burden of disease, but is served by just 3% of the world's health workers, with access to 1% of global health expenditure[31]. To succeed, telehealth must focus on very specific and evidence-based needs of each region including the shortage of health workers and the required skills upgrades to allow the developing world to establish its own experts. It must also overcome the current issues with implementation in the developing world, including limited resources, unreliable power, poor connectivity, and the high cost for poorer members of society (those often the most in need) [32].

Any research policy and action plan must include an EU- and world-wide dialogue. Opportunities are created by international fora and cooperation, with EU leadership.

3.2. A multi-generational population with age-specific needs

An ageing population is often cited as a core challenge facing Member State health systems. However, other age groups also warrant particular attention. Improved care has meant that children with congenital diseases survive longer, and will therefore require special support as adolescents and adults, as well as an increased understanding of how their conditions interact with other diseases.

Taking a lifecycle approach, with an increased focus on child health and pregnant women's health, may offer opportunities to address acquired life-style related disease. As new interventions become tailored to the individual, child and age-specific guidance should be further developed.

Every EU Member State (MS) faces the challenge of an ageing population, with the population aged 65 and over in the WHO European Region predicted to rise to 224 million by 2050[33]. This ageing is driven by four main factors: declines in old age mortality; declining birth rates; the ageing of the baby boomers; and insufficient immigration to rebalance the demographics. In particular, it is the reduction in old-age mortality (life expectancy at 65 in the EU is now 17.9 years for men and 21.3 years for women[34]), driven largely by improvements in medical care, which has meant the EU's population has become increasingly elderly[35].

In addition to the issues associated with an ageing population, child mortality rates have significantly decreased, meaning more children are surviving into adolescence and adulthood. For example, between 1990 and 2015, the global under-five mortality rate more than halved, dropping from 90 to 43 deaths per 1000 live births[36]. Although reductions in deaths from pneumonia, diarrhoea and measles accounted for 47% of this reduction between 2000 and 2013, there has also been an annual decrease of 0.8% between 2000 and 2013 in neonatal congenital diseases[37].

More specifically, due to the advent of cardiothoracic surgery, 90% of children born with congenital heart disease (CHD), the most common inborn defect, now survive into adult life, compared to only 20% in the 1950s. Individuals now require additional support to manage recurring medical issues from their condition throughout their life, and healthcare needs to take a lifecycle approach, considering pre-existing conditions and their interactions with new diseases or lifestyle factors. For example, even CHD patients who have undergone surgery may have significant haemodynamic impediment, suffer from Eisenmenger's syndrome, infective endocarditis, or have problems regarding conception and cardiac disease during pregnancy[38].

Taking a lifecycle approach may also offer opportunities to address the causal pathways of chronic disease. There is growing evidence that developmental plasticity processes (in addition to variation in individual genotype and lifestyle) may explain the individual variation in the risk of developing obesity and other chronic diseases in an obesogenic environment. For example, there is evidence that prenatal undernutrition and stresses that lead the foetus to predict an adverse future environment, can lead individuals to develop with central and peripheral changes that increase their sensitivity to an obesogenic environment. Maternal obesity and diabetes, and infant overfeeding are also associated with a greater risk of later life obesity[39].

There is also a need to take a more age-specific approach to health and disease. For example, an April 2015 study concluded that statin therapy recommendations in the US for cholesterol treatment could be improved by using the individualized age and sex-specific CVD risk thresholds rather than the currently used 10-year fixed risk threshold[40]. Using age-specific approaches may be particularly beneficial for mental health and degenerative diseases which often have age-specific clinical presentations, treatment responses and side-effect concerns. Age-specific presentations of disease may also have different causal pathways, for example, genetic influences are probably less in older patients with bipolar disorder compared to younger patients, meaning treatment options will differ by age[41].

Major societal and medical challenges, such as obesity, mental health and degenerative disease, require age-specific approaches.

3.3. Genes, environment and life-style - 'Big Data' for health

Traditional disease classification and approaches, symptom-based and organ-centered, are no longer valid. The presentation of disease is changing (multi-morbidity, complexity of disease) and shared mechanisms such as inflammation and abnormal immune responses are recognized. Growing knowledge demonstrates the need for a new approach to health and disease based on causative pathways that include genes, environment and life-style, with treatment according to etiology, often with multiple dimensions. Health interventions will become increasingly personal.

Novel technologies, cloud-computing and shared platforms will generate comprehensive datasets that cover a multitude of information on one individual, as well as large datasets across individuals in an array of domains.

With the opportunity for collecting such large, comprehensive 'Big Data' comes the challenge of harnessing this information. A comprehensive, holistic approach calls for multi-disciplinary research and further development of novel disciplines such as systems biology and evolutionary medicine.

The potential created by this approach offers opportunities for:

- Pre-emptive and improved preventative approaches targeting health; and
- Tailored treatments aiming for precision medicine

Research must explore the feasibility and affordability of the expectations created by these opportunities. A challenge here is the design of studies that provide evidence for approaches that target small populations, as is currently already the case for rare diseases.

Chronic disease and multi-morbidity, defined as the co-occurrence of two or more chronic conditions in one persons, are becoming increasing problems as a result of Europe's ageing population – two-thirds of Europeans nearing retirement age are living with two or more long-term conditions[42]. Chronic disease and multi-morbidity not only affect mortality; they affect quality of life, ability to work and employability, and currently clinicians have limited guidance or evidence on how to work with such patients, and how to develop effective care plans[43, 44]. As Boyd & Fortin (2010)[45] argue, healthcare is currently too focused on a single disease approach and polypharmacy, which are associated with greater levels of adverse effects and drug interactions.

Boyd & Fortin (2010)[46] also argue that considering multi-morbidity is essential when designing and evaluating health systems: understanding how to deliver this care in an effective and efficient way is an "enormous challenge" but also a great opportunity for clinicians, researchers and policy makers today. Currently, across Member States, the disease-based focus prevails, and is influencing the design of clinical trials right through to the reimbursement structure for healthcare. It is important that healthcare systems recognize that some health problems are the consequences of multi-morbidity and not diseases per se, and patients should receive a patient and family-centred approach to care. This should also include understanding how health, social care and voluntary sector services can work together to offer integrated, holistic care[47, 48] .

The more science understands about a person's biological makeup, the more it becomes clear that many causes of disease, along with the reasons why many patients do not respond to treatment (or why they suffer serious side effects) can be explained by the variability in an individual's characteristics[49]. Personalised medicine aims to tackle these problems by moving away from a 'one size fits all approach', by integrating data on the entire dynamic biological makeup of each individual, as well as the lifestyle and environmental factors that interact with this makeup to develop a complex and individual phenotype. This integrated information can then be used to make models to identify the most appropriate healthcare for individual citizens.

However, before the potential of personalised medicine can be realised, research will need to move away from focusing on symptom combinations or a particular organ or system, and instead begin to integrate population-level genetic, lifestyle and environmental data to understand in more detail how these interactions shape individual responses to disease and treatment[50]. The "P4 revolution" (medicine that is Predictive, Preventative, Personalised and Participatory) will emerge from taking a multi-disciplinary approach, combining systems biology with the ability of the digital revolution to develop consumer devices, generate and analyse "big data" sets and disseminate this information via business and social networks[51].

Six actions have been identified to maximize the potential of personalized medicine in the EU. The EU has already shown progress towards some of these actions, but lags in others. Necessary actions include[52]:

- *Combine and coordinate cross-country expertise on technology development (this includes the optimization and harmonization of analytical platforms which use high fidelity imaging to identify biomarkers of exposure and response, to develop diagnostic tests).*
- *Harness large, well phenotyped birth, cross-sectional, longitudinal and disease cohorts across the EU.*
- *Generate high quality data and bio-resources or biobanks relating to individual disease areas, which can be linked to contextual information on environmental variables, lifestyle, nutrition, etc.*
- *Develop the necessary interdisciplinary environment by breaking down existing barriers that separate biological, physical, social, economic and political sciences, particularly focusing on joining mathematical and computational skills to the biological sciences.*
- *Develop new precision diagnostics and targeted therapeutics through engaging a wide range of industries, particularly SMEs.*
- *Raise awareness of P4 medicine among the wider health and medical communities. This includes appropriate training and education programmes to ensure there are trained professionals to support the implementation of personalized medicine, as well as improving the health literacy of the wider population.*

A number of breakthroughs have already been observed from using comprehensive, shared datasets, mainly for cancer, but also other diseases e.g. for HIV.

There are a number of large cohort studies that will provide strong population data, e.g. the European Prospective Investigation into Cancer and Nutrition (EPIC) study[53] (521,000 participants across 10 European countries, studied over 15 years; one of the largest cohort studies in the world) and The Nurses Health Study[54], (information provided by 238,000 nurses since 1976). Additionally, large bio-resources and biobanks also exist, for the Global HIV Vaccine Research Cryorepository, a bank for unique viruses and reagents for vaccine research.

The International Rare Diseases Consortium[55] is an example of pooling data and research efforts to increase power in a global and multidisciplinary approach. However, further developments are needed as currently multi-disciplinary initiatives are rare, and tend to be national, rather than EU-wide, in scope.

'Big Data' for individuals and populations creates expectations for revolutions in health, including personalized and precision medicine. Further research on benefits and feasibility is needed and will require an expert workforce in a collaborative approach.

3.4. Smart and 'disruptive' technologies

Novel technologies are developed at high speed, not necessarily in sync with medical or societal needs, and offer novel opportunities, which in turn need research to evaluate their potential benefit and risk.

Likely areas for further development with high impact include the wide availability of high speed genetic sequencing, a growing number of intelligent materials, 3D printing, surgical robotics and internet-based support for homes. Each of these 'disruptive' technologies will require further research.

An adaptive legal and ethical framework is needed to support this flow and to ensure safe further development and "unexpected" discoveries, without hindrance to implementation.

There are numerous examples of new, disruptive, technologies and their use in health and social care settings. For example:

- *There is a focus, under Horizon 2020, on the use of technologies in independent living. For example, the EU-funded project Giraff Plus is testing out the use of robotics in helping elderly people who want to stay at home[56]. A multi sensitive and immersive internet has the potential to be accessed through many different types of devices allowing greater individual control over health[57].*
- *3D printing has a huge potential in medicine: from prosthetics, to the bio printing of cells, to lifelike models of organs to the possibility of printable, implantable tissue[58]. For example in Spain in September 2015 the first 3D printed sternum and rib cage was implanted into patient that had suffered from a cancer tumour that had grown around his ribcage.*
- *More advanced forms of chemical, genetic, technological and physical upgrades of individuals are thought to be within reach[59]. For example, the Global Future 2045 Avatar project is working in the field of life extension by means of the cybernetic technologies[60]. There are three main phases; a humanoid robot with a brain computer interface system, a life support system for the human brain and finally an artificial brain in which to transfer the original individual consciousness into[61].*

However, the emergence of new disruptive health technologies also raises practical, theoretical and ethical concerns. The European Group on Ethics in Science and New Technologies (EGESNT) highlights that there has been a 'participatory turn' in health. New technologies and data are altering what it means to be a patient and there is an opening of new roles to citizens in the production of medical knowledge and innovation[62]. People now volunteer data; non-experts are involved in scientific experimentation and analysis; and the lobbying efforts of interest groups and public input into research and funding can shape the formulation and regulation of polices'[63]. Health and healthcare are being perceived, organised and delivered differently[64]: individuals are shifting their views of health, their body and conceptions of illness and disease[65]. These shifts give rise to a number of ethical implications, including: balancing autonomy and responsibility between the state and the citizen; disentangling participation of citizens from exploitation; and managing the potentially unequal participation in, and access of citizens to personalised health technology[66]. Furthermore, smart technologies can undermine, reconfigure and overrule legal certainty and threaten privacy, identity, autonomy and non-discrimination[67].

Recommendations to mediate these risks include: raising awareness and education around these issues; adding citizen rights in EU policy health data; and the maintenance of non-ICT based alternatives of healthcare so that citizens who do not, or cannot, participate in new health technologies are not left untreated[68]. Smart technologies' potential to threaten privacy should be countered by cooperation between lawyers, computer scientists and civil society to engage with these technologies and reinvent laws surrounding these areas[69].

Exciting revolutionary technology is booming but its impact on health and healthcare needs to be evaluated through proper research, within a balanced and constructive regulatory framework.

3.5. 'Open Science' and data integrity

Better access to research data can multiply the benefit of investment. Challenges for implementation are data management, data curation, exchange protocols and continuity.

Importantly, a plethora of low quality information is likely to be hampering, rather than supporting, progress.

The problem of data and scientific integrity is growing. In 2011, the ESF released 'Forward Look: Implementation of Research in Clinical Practice', a key theme of which was the wastefulness of scientific research due to poor design protocols, lack of reproducibility and failure to systematically review existing evidence before starting new research. More recently, at the end of 2015, the Lancet published a special issue discussing the value of research and reducing scientific waste, and in 2014, the NIH held a joint workshop with the Nature Publishing Group and Science, attended by representatives from 30 research journals, where the rigour of research findings and reproducibility were discussed[70]. As a result, the journals agreed to adhere to various guidelines to ensure the robustness of the research results they report.

Most recently, in December 2015, Science Europe published a comprehensive review of developments in research integrity across Europe and the US[71], arguing that:

"…research integrity is at the core of science and scholarship. It is the basis for researchers to trust in each other as well as in the research recorded. Equally importantly, it is the basis of society's trust in the research system".

The report argues that research misconduct currently occurs at too high a rate. For example, in 2012, from all sources, the US NIH Office of Research Integrity (ORI) received 423 allegations of misconduct, an increase of 56% compared to 2011, and much higher than the 1992-2007 average of 198. Overall, 40% of these cases were deemed evidence of research misconduct, slightly above the historical annuals average of 36% of cases investigated. In addition, these statistics do not reflect the increasing body of evidence of the under-reporting of both serious misconduct and questionable research practices by individuals and institutions.

The research suggests that research misconduct could be reduced by altering the career and advancement system for researchers; ensuring proper control and evaluation mechanisms that allow researchers to better police themselves; providing standardized training in research integrity; and most importantly, ensuring European and/or international research integrity standards. This includes ensuring a common EU-wide framework for systematic reviews and an agreed structure on the processes that need to be followed to achieve the best evidence[72]. Horizon 2020 is the first EU research Framework Programme in which the Rules of Participation explicitly mention research integrity and there is currently no agreement across Europe about the best national regulatory frameworks for research integrity, with only half of European countries having specific legislation to deal with misconduct[73].

However, arguably the most important way to ensure scientific integrity, is through the proper management of "big data". As the 2015 Science Europe report states:

"The quality and reliability of the available research data will be entirely dependent on the capacity of researchers and their institutions to manage, curate and preserve potentially very large or complex data sets".

There also needs to be common guidance on how to ensure acceptable levels of transparency and mechanisms to keep track of all human studies that do not get published. This view is supported by the WHO, which highlights the need for registering all clinical trials in a free, publicly available, searchable registry that is regularly updated[74]. Smaller-scale examples of such a database are already in existence, for example the EORTC Clinical Trials Database which contains information about clinical trials conducted by the European Organisation for Research and Treatment of Cancer and clinical trials from other organisations with EORTC. At a European level, the European Clinical Trials Database (EudraCT)[75] is now available and is the first example of a publicly available database of all clinical trial summary results in Europe. At an international level, AllTrials[76,77] is currently campaigning for all past and present clinical trials to be registered and their full methods and summary results reported.

In addition to increased transparency of clinical trials data, according to the European Science Foundation, "the move to make peer review journal papers openly and freely available through Open Access (OA) has been one of the most significant and positive developments in publishing in recent years". In 2013, of the 2 million articles that were published, just under 300,000 were open access and Elsevier published more than 6000 'gold' open access articles[78]. The ambition of many funding agencies across Europe, including the European Commission and Science Europe members) is to have a fully OA system of publication in the future, something that has already been achieved by the NIH, which requires OA availability of results from the research projects they fund. Achieving this aim will require not only funding agencies and publishers, but also political commitment and influence.

The 2015 Science Europe report conclusion highlights that "research integrity has the potential to increase the quality of research in the European research ecosystem, thereby increasing its overall effectiveness and impact into the future". Carlos Moedas, European Commissioner for Research, Innovation and Science, has also highlighted open, transparent research as one of three key priorities, in his June 2015 Speech, 'Open Innovation, Open Science, Open to the World'.

The integrity of data needs to be safeguarded from the source through to reporting and publication. This should take place within a culture of scientific integrity, transparency and open access.

3.6. Digital Health

The integrated use of Information and Communication Technology (ICT) for the design, support and networking of all data, processes and participants in European healthcare has huge potential. It will contribute to improving the health literacy of Europe's citizens, and will improve diagnosis and treatment outcomes, for example through the use of Precision Medicine and Telemedicine. Digital Health technologies will also improve economic productivity for health organisations and professionals, in both traditional and new health markets, through (bio)medical technology transfers, novel business opportunities, venture investments and the development of leading promising start-ups.

A science-led research programme for Digital Health which focusses on: the impact of digitalization and electronic integration (internetting); patients' values and needs; and medical services, ethics and public health will create and enforce equal standards for the use, implementation and distribution of Digital Health.

Health data are increasingly becoming available in digital form. This is particularly true for precise diagnostic data, such as those obtained by vital signs monitoring, radiological and pathological imaging, and genetic information, including whole genome sequencing. Data can be collected in the hospital, but also in decentralized settings, including in the home. Data, and actionable information and insights derived from them, can then be shared amongst the different healthcare professionals across the care continuum. For example, Apple's health kit app[79] transmits health data through mobile devices, integrating it into large IT health systems that medical professionals can access. In New Orleans, the app has been used to monitor weight increase in patients with heart problems and subsequently the data is used by pharmacists to change drug prescriptions to treat the patients changing needs[80].

Data can also be used by individuals themselves to help self-manage their condition, modify their behaviour, and engage in decisions about their care. Access to information that is comprehensive, reliable and individualized is key to this. For example, in 2011 LG Electronics launched 'smart refrigerators'[81] where people can track their nutrition intake and Google are developing the 'smart contact lens'[82] that will be able to monitor blood glucose levels in diabetic patients. Health literacy can also be improved through access to data and the internet, for example through websites such as Doctors on Demand[83], where patients can access advice online and have immediate video consultations with doctors – although challenges arise here in ensuring quality control, and equality of access[84].

Digital Health reaches across medical platforms and smart technologies to enhance health promotion, prevention and health care. A comprehensive European research policy is needed that enables the implementation of digital technologies and the reliable flow of data.

3.7. A diversity of stakeholders for research without boundaries

Biomedical research is already multidisciplinary, incorporating medical sciences, physics, chemistry, bioengineering, and information technology. However, to ensure a truly holistic approach, it needs to be expanded to include studies on climate, security etc.

The chain from exploratory research to innovation and implementation in health care involves multiple stakeholders with different goals and expectations including: scientists and health care professionals, government and public funders, private enterprises, patients and society at large. Although an ongoing challenge, this also affords opportunities for shared responsibilities and novel models of collaboration, not only public-private, but also within the private sector.

The research and development process, from initial development of ideas through to final implementation requires the interaction and collaboration of an increasing number of stakeholders. As healthcare moves into a world of personalised medicine and "big data", cross-disciplinary interaction becomes increasingly important. For example, the European Science Foundation, in their foreword on personalised medicine for European citizens clearly highlights the need for clinicians to work together with bio-scientists and technologists to develop the tools required for personalised medicine[85]. Within this area of research, bio-scientists need to understand what information the clinicians need in order to provide the best treatments to patients, and technologists must understand the needs and interactions between healthcare professionals and patients so that tools have appropriate interfaces[86].

In addition to funders, scientists and clinicians, patients are becoming key stakeholders in the research and development process, thanks to the rapid expansion of personalised digital health technologies. The Agency for Healthcare Research and Quality in the US emphasises the way that consumers, patients, caregivers and patient advocacy organisations are now playing an increasingly important role in the dialogue with healthcare professionals so that their needs are understood and addressed[87]. Furthermore, one of the NIHR Biomedical Research Council's (BRC) core aims is around inventions and interventions that are valued by patients and the public in terms of feasibility, acceptability and potential efficacy[88]. For example, one of BRC's objectives is to create an interactive web application for patients to be able to access their health records that they can use to prepare for meetings with clinicians[89].

In addition to increasing patient involvement, public sector organisations are also getting more involved in research and development activities, particularly through policy and advocacy work, increasing the power of the public over national and international decisions in health. For example the Wellcome Trust works with policy makers in the UK and internationally to ensure that the funding and regulatory environment enables biomedical research to maximise its benefits for health[90]. One of their successful achievements was to get the UK Parliament to amend the Human Fertilisation and Embryology Act 2008 to allow mitochondrial donation[91].

However, in any attempt for collaboration, there are always conflicts of interest between different stakeholder groups, which must be addressed and managed. The IMI[92], a collaboration between a wide range of different partners including patients, the pharmaceutical industry, academic research centres, health care providers, and regulators[93] has had to overcome some professional and cultural differences between individuals working in the different sectors. More specifically, issues over Intellectual Property in both the university and SME/pharma sectors can often interfere with the speed with which novel exploratory approaches involving different stakeholders can proceed[94].

The race to sequence the human genome is another example of conflict of interest between stakeholders with different goals and expectations. The main area of conflict occurred between the private company Celera wanting to patent some of the genome sequences, which could have meant that the results of the work, leading onto diagnostic tests and potential cures for genetic disease, would have been owned by them[95]. This would have constricted further research and went against the public funded project notions that any sequence obtained would be made available to anyone via the internet[96]. The final project was a successful collaboration between national government funds, predominantly the US, and public organisations such as the Wellcome Trust from the UK, which meant that data remained publicly accessible. This private/public debate around data access is an increasingly important issue as more and more patient data becomes available and more private multi-national companies such as Google and Apple become involved in developing new digital technologies.

Overall, multi-disciplinary collaboration can be successful but needs careful preparation. There needs to be more focus on identifying a "precompetitive space" that allows for innovation, especially between a number of collaborating partners[97]. GlaxoSmithKline provides a good example of how a private sector, downstream organisation can cross-collaborate with academics from all over the world. More specifically, GSK has over 500 active collaborations with more than 50 UK universities; collaborations in many other European countries, the largest number in Germany, France, Switzerland and Ireland; and agreements in 23 US states[98]. As well as collaborations with institutions, GSK also co-funds around 240 PhD students in the UK, mostly in partnership with three key Research Councils (the BBSRC, EPSRC and MRC)[99] and over 30 new studentships co-funded with Research Councils were formed in 2013[100]. Their main recent innovation in academic collaboration is the Discovery Partnerships with Academia Model (DPAc), with the aim of bringing together GSK's drug discovery expertise with 11 academic partnerships[101].

Another example of multi-disciplinary collaboration is Roche's active reach-out program for collaborative innovation. Over the last six years they have collaborated with 50 universities worldwide, and since 2009, nine new companies have been founded as a result of their work, and four collaborative projects have been internalised[102].

Novel models of cross-border research involving different stakeholders enrich health research. However, they require a comprehensive policy where patients and the wider society are actively involved, setting common goals.

3.8. Expecting the unexpected

One of the challenges is the lack of predictability of 'new' diseases, e.g. re-emerging infectious disease, catastrophic events, or the 'unknown'. This requires flexibility and openness, balance between strategic agendas and bottom-up initiatives.

Progress still needs to be made in predicting new and unexpected health threats. The international response to the 2014-15 Ebola epidemic in Western Africa highlighted a number of current structural failings, with a recent November 2015 Lancet article reporting that the epidemic revealed "deep inadequacies"[103] in national and international institutions responses to outbreaks of infectious disease.

In order to improve international responses, the article recommends the formation of a dedicated centre for outbreak response under the WHO that is fed into by governments, the scientific research community, industry and non-governmental organisations[104]. The EU commission's council on lessons learned for public health from the Ebola outbreak in West Africa also stressed many areas of improvements to health security within the EU. These include improvements of cross sectoral coordination and collaboration in facing public health emergencies of international concern within the EU; the strengthening of preparedness research, notably with regard to diagnostic methods, vaccines and therapeutic products development; and improvement of coordination between the European and global research community[105].

4. STRENGTHS OF EUROPE

4.1. Excellence of research and forefront developments

The EU27 scores above the world level in impact, with a leading position in a number of areas, e.g. EU teams have led successful, large-scale, worldwide projects in genomics and neuroscience. The European Research Council gives support to the most creative ideas and outstanding research.

The current -omics drive was started in Europe and is supported by excellent facilities for genomics, metabolomics and, more recently, systems biology.

Europe has strong academic and research institutes, with international networks. Around these, hubs of public-private partnership and innovation have emerged, and Europe has a strong biotech landscape. Europe also has leading industry in diagnostics, medical and health technology.

Several disciplines have achieved integration of world-class research in top institutes and agencies at European level e.g. physics (CERN) and molecular biology (EMBL), but also space research (ESA), astronomy, and climate research. Health and biomedical research aspire to nothing less.

The EU is one of the world's main knowledge production centres and accounts for almost a third of the world's science and technology production[106]. The research and knowledge produced is innovative, and impactful. In the most recent Global Innovation Index results (2015)[107] three EU Countries (the UK, Sweden and the Netherlands) were named in the world's five most innovative nations, and the UK, Italy and Germany all scored higher than the USA for citation impact, with France also scoring above the world average[108]. Furthermore, 33,000 ERC-funded articles are listed on the Thomson Reuters' Web of Science, with 7% of publications among the top 1% most highly cited in their discipline.

This high quality research is driven by Europe's strong academic and research institutes. Four of the top ten universities in the world are based in Europe[109] and independent research institutes, for example, the Max Planck[110] groups in Germany, and INSERM[111] in France, are internationally renowned. There are also examples of small, dedicated institutes which are publically and privately funded, such as Champalimaud[112] in Portugal and CNIC[113] in Spain. However, most of these centres work within MS, rather than across. There are examples of collaborative working (for example through the Health Axis Europe, a strategic alliance formed between biomedical clusters in Cambridge, Leuven, Heidelberg, Maastricht and Copenhagen[114]), and centres that reach out beyond Europe (e.g. the Fraunhoffer Institute[115]), but most research centres work within individual MS, not internationally. Nevertheless, in some areas, true European institutes exist, integrating world-class research, such as CERN, the ESA, and EMBL.

European health and biomedical research is world-leading, and rapidly developing in a number of sectors. Genomics and stem cell research is well-established, and a number of European Centres (such as the Sanger Institute in Cambridge, and the Luxembourg Centre for Systems Biomedicine) are world renowned. In genomics, the introduction of the 100,000 Genomes Project in 2014[116] has made the UK the world leader in ground-breaking research into cancer and rare diseases; while in stem cell research, European researchers have led on the development of regenerative medicine, reproductive health, and genetic disease[117] – for example, pioneering the transplantation of photoreceptor nerve cells and adult retinal stem cells to help people with degenerative eye diseases[118].

In addition, the European biotechnology sector is developing rapidly, with the medical technology market now estimated at roughly EUR 100 billion, the second largest in the world (after the US). The industry employs over 575,000 people, 50,000 more than the US. In 2014, more than 11,000 medical technology patent applications were filed with the European Patent Office (EPO), more than any other sector in Europe, and double the number since last decade[119]. Some of this development has been driven by improved investment, leading to increasing numbers of biotech companies. In 2014, nearly EUR 2.5 billion was invested in new biotech companies (25% more than 2013), and three times as many companies (13)

went public than in 2013. By the end of 2014, there were 150 publically listed biotech companies worth EUR 66 billion[120].

4.2. An organised health care system fuels the potential of Digital Health

In line with the priority of health for all, Europe has publicly supported and organized health care with implementation of evidence-based medicine (EBM). Patient records and centralized databases can be used to support clinical research (patient recruitment, outcome research).

Europe has strong expertise in clinical trials with extensive databases. Its population is engaged and willing to participate in research and contributes to rich collections of population cohorts with extensive data, including annotated biobanks with long-term follow-up. Patient participation in clinical research is growing.

Europe ensures equal access for patients to reliable health information and communication. Ethical rules on the quality, and therefore the credibility of, content and content providers will be created under ethical governance in Digital Health, "Made in Europe".

Europe can gain decisively with respect to the United States, and their well-known global players in the Digital Health arena; visionaries such as Google, Apple, IBM, GE and others. They can re-take a leading position in the up-to-date connectivity of health and research across all Member States and in health data management, by combining structured data (public health data) and non-structured data (m-health data), primarily for user/patient safety processes and outcomes online.

As the ESF highlights: 'as a result of previous European research investment and the particular organisation of healthcare within Europe, many of the world's most valuable patient and population cohorts are located in European countries[121]'. These include some of the largest cohort population databases in the world (such as the European Prospective Investigation into Cancer and Nutrition (EPIC)[122], and the Nurses Health Study), and a range of biobanks. There are several examples of European research and innovation building on these strengths:

- *The EU has been developing Electronic Health Records (EHR) since 2004 and is one of the leaders in the EHR global race[123]. Initial results from the European Patient Smart Open Services (epSOS) are being used to create initiatives such as EXPAND, which is building upon the epSOS infrastructure to progress to sustainable cross border eHealth services at EU and national level[124].*
- *Europe has some of the most extensive biobanks available worldwide. Projects such as BBMRI-LPC biobank (which involves 30 partners from 17 countries, with 22 cohorts) aim to capitalise on these by improving the harmonisation and collaboration between different biobanks and researchers. The biobank will unite the large prospective study datasets in Europe, harmonising the collected samples and data 'to tune them up for ground-breaking science'; facilitate collaborative transnational research; and provide a networking platform for established and emerging biobanks[125].*

New areas of digital health development, such as telemedicine, are also taking advantage of large, multi-national datasets. For example, the Renewing Health project included a randomised clinical trial (RCT) with about 7,000 patients from nine European regions[126].

4.3. Public funding, support and engagement

At this time the public funding for biomedical research is still substantial even if overall below the targets. The benefit of research to society is recognized and ensures public support for this investment.

Nevertheless, the funding is fragmented with a range of funding sources (e.g. charity, public, private), fragmented within Europe, and balancing bottom-up and directed research, explorative/basic and applied research.

The Innovative Medicines Agency (IMI) initiative is a good example of collaboration between a wide range of different stakeholders and funding, including patients, pharmaceutical industry, biotech companies, academic research centres, health care providers, regulators, etc.

Healthcare expenditure is large, on average exceeding 10% of public spending, and reflects the value and importance of health, but also contrasts with the much smaller investment in health research[127].

In the EU, the majority of funding for research and development in health is provided by the private sector. For example, of the approximately EUR 47 billion invested in research and development in health in 2011, 60% was provided by the private sector (mainly pharmaceutical companies), while 40% was provided by individual Member States and EU institutions[127]. More specifically, funding sources include:

- *The European Commission. Under Horizon 2020 the 7-year budget for the societal challenge 'Health, demographic change and wellbeing' provides EUR 7.2 billion for research. Various other programmes will also include health research. The Horizon 2020 'Excellent Science' funding stream will invest EUR 24.4 billion in various large-scale initiatives including the activities of the European Research Council on future research, while the 'Innovation in SMEs' will include support to biotech. The current Health Programme under DG Health and Food Safety, running from 2014-2020, has a total budget of EUR 449.4 million.*
- *Individual Member States. Within Europe the largest investors are Germany, followed by France, the UK, Switzerland and Italy[128].*
- *The research-based pharmaceutical industry. This sector has invested about €30 billion in R&D each year in Europe alone, employing 700,000 people and generating three to four times that number of indirect jobs[129].*
- *Universities, independent research institutes and other private enterprises; and*
- *Charitable and non-profit organisations e.g. the Wellcome Trust.*

With a predicted increase in European healthcare investment (by 2030, total healthcare expenditure is predicted to rise by 5% of Europe's GDP, to 13-18%[130]), the current funding and its structure need to be addressed. At present, sources of investment are too fragmented with the EFPIA arguing that "coordinating nationally fragmented policies under a world class, pan-European R&D agenda is one of the keys to creating critical mass and competitiveness in the field of innovation and ensuring a viable, vibrant European healthcare ecosystem"[131].

Currently cross-border collaboration is limited, this is both caused by, and causes, fragmentation. Whilst some areas of Europe perform very strongly (eight of the top ten global innovation countries are European[132]), countries in Eastern Europe and some southern European countries are lagging behind. As highlighted above, a diversity of research funding sources can also limit the development of a clear vision; this is exacerbated as different MS have different funding policies and targets. For example, in the UK the largest share of research funds is channelled through universities, whilst in France, government research organisations such as INSERM (Institut National de la Santé et de la Recherche Médicale) and CNRS (Centre National de la Recherche Scientifique) are core recipients. There are also differing values across MS regarding approaches to healthcare and research, with some countries focussing more on ensuring managerial, economical and regulatory efficiency in healthcare systems (for example, the UK) and others focussing on the more medical aspects (for example, France)[133]. These differences can also lead to differing priorities for biomedical research and healthcare, and to fragmented approaches.

Increasingly, the EU is trying to fund research which crosses sectoral boundaries. For example, the Innovative Medicines Initiative (IMI) and the IMI2 are a joint undertaking between the EU and the European Federation of Pharmaceutical Industries and Associates (EFPIA). They aim to support a collaborative pharmaceutical R&D ecosystem in Europe that will lead to quicker, more efficient discovery and development of better and safer medicines for patients. The projects have a €2 billion budget and act as a catalyst for partnership working, bringing together competing pharmaceutical companies to work with each other and with universities, public laboratories, regulatory agencies, innovative SMEs and patient's organisations. IMI 2 will particularly focus on developing next-generation vaccines, medicines

and treatments e.g. new antibiotics, while its strategic component centres on personalised healthcare.

4.4. Education

Europeans have good access to education, particularly at higher levels. The number of scientists has been growing and scientific output has increased accordingly.

Although the number of R&D researchers per million of the population still lags behind the US[134], the number of researchers in the EU-28 is increasing. The number of researchers increased by 500,000 (or 41%) in the ten years between 2003 and 2013, to 1.73 million (in full-time equivalents). More than 73 million people were employed in science and technology occupations in 2013, equivalent to one third of total employment. The pipeline of future scientists is also strong. Within the EU-28 in 2012 there were 17.1 graduates in mathematics, science and technology per 1000 persons (aged 20 to 29); and there were an estimated 717 000 doctoral students in the EU-28 in 2012, compared with 492 thousand in the US and 75 thousand in Japan.

While it is acknowledged that current health research education in Europe may not instil the necessary skills and mindsets needed to foster innovation, the EU is supporting programmes such as the European Institute of Innovation and Technology (EIT)[135] to further develop entrepreneurship across curricula.

5. THE WAY FORWARD

As evidenced in the preceding sections, there is excellent research potential in Europe to address the challenges ahead. However, there is a need for action as there are a number of weaknesses that are holding back progress. Innovation is slowing down and competitiveness is at risk with research(ers), biotech and industry leaving Europe.

A number of reasons have been cited for this. They relate to the political and regulatory environment, the pressure for rapid return on investment (in public and private enterprise), a workforce not adapted to the new demands and lack of investment. These specific issues require specific solutions but specific solutions need to be developed within a comprehensive framework that is currently lacking.

Indeed, cutting across these issues is a lack of coordination and vision at European level for biomedical and health research. Policy, authority and decision-making are divided between Member States and the EU, and any vision and potential solutions remain fragmented, addressing specific issues but not formulating a long-term comprehensive strategy. This is in contrast to e.g. the National Institute for Health, USA, where roadmaps are laid down and reviewed on a regular basis with broad consultation.

Reversal of fragmentation, responsible for loss of research potential and innovation, and leadership are needed. This requires intensified cross-border collaboration and development of a comprehensive long-term vision to underpin it.

This vision aligns well with the priorities set by Carlos Moedas (Commissioner for Research, Science and Innovation), in his 2015 speech entitled 'Open Innovation, Open Science, Open to the World'[136], which highlighted the need to involve all stakeholders in research, including members of the public; facilitate open access to all publications and data produced; and the importance of gaining a global competitive advantage for EU science through science diplomacy and collaboration. The Commissioner further emphasized the importance of health research during the SPH conference[6] and the need for action.

How to advance and boost health research

- facilitate high quality cross-border collaboration within Europe and beyond
- nurture multi-stakeholder research across the innovation cycle and find common goals
- integrate and assess the potential of novel and disruptive technologies
- ensure a comprehensive and aligned, facilitating regulatory framework
- involve citizens and patients
- create value, through health, and a knowledge-based society

5.1. Facilitate high-quality cross-border research within Europe and beyond

The EU-funded collaborative projects are examples of success but represent only a fraction (< 10%) of funding for biomedical and research. Despite subscription to the ERA by the EU members, research remains largely a matter for MS, and inter-national competition, limited shared resources and limited common investments prevail.

- Advancing biomedical and health research will need enhanced support for cross-border research activities. The implementation should be based on the highest standards available and promote excellence. National funding mechanisms in some European Countries are still to be improved with respect to quality, quantity and competitiveness. Novel cross-border funding schemes should concern not only public funding but also collaboration with and within the private sector and should focus on collaborative research that adds value and is complementary to or beyond national research initiatives.
- Future cross-border collaborations should build on the successes of current collaborative work and smaller-scale projects, and on mutual trust in the joint investment. Examples of how to incite novel cross-border collaborations with supportive funding already exist (NordForsk[137], for example). Some are EU-led, such as the initiatives under article 185 for collaboration within and outside Europe (e.g. AAL and EDCTP[138]), or agreements between the EU and other agencies, e.g. NIH[139]. Others are bottom-up initiatives such as Cancer Core Europe[140].
- For cross-border collaboration, legal, technical and organisational barriers need to be addressed.
- 'Big data' can be generated through cross-border collaboration. 'Big data' is not a substitute but a rich supplement to traditional data collection and analysis requiring proper infrastructure and access. Enabling the exchange of knowledge requires common standards for data sharing & data linking. Further innovation is needed for proper curation, storage and analysis of big data across nations.

5.2. Enhance collaboration and alignment across the innovation cycle and health care

The investment in and strategic priorities for biomedical and health research are decided in many fora along the innovation cycle. Currently, academia, SMEs, and large pharmaceutical companies often work in different stages of research. There is a 'huge gap' between the capabilities of small biotech companies, academic consortia, and big pharmaceutical companies. There is further potential in addressing academic mind-set and training, in bringing research into health care and attracting private investment. A diverse portfolio of funding and training opportunities needs to be created across the innovation cycle.

- The cost of health care is two orders of magnitude higher than the investment in research. Yet, in particular in the stage of therapy development and evaluation, the activity of research and treatment is interwoven, performed or at least organized by the same professionals and within the same premises. A more intense interaction and cross-funding must be stimulated, taking cues from current initiatives[141],[142],[143].
- For successful collaboration across business, academia and industry, cultural differences, complementarity in skills and knowledge need to be acknowledged and common goals need to be defined. Deliverables must be clear from the beginning of the process and remuneration rules must be in place. Exchange programs for training and mixed careers are tools to facilitate collaboration.
- European researchers and research institutions need to learn more about how to successfully qualify for and negotiate terms for private equity investment. Education and training must diversify and include tracks to build entrepreneurial mindsets and skills; as well as, to understand what reliable, robust and in-depth research data is needed to present to external investors. Partnership in building programs[144] is essential.
- Europe can do more to incentivize industry experts to engage in biotech start-ups or to attract successful managers.
- The core disciplinary knowledge in Europe is exceptional, however, further efforts are needed to break down silos between disciplines towards establishing truly

multidisciplinary research beyond current collaborations of life sciences, engineering & natural sciences). Cross-border collaboration of independent teams has to expand into new areas such as environmental studies, social sciences, ethics and law[144].

5.3. A comprehensive and facilitating regulatory framework

Novel research paradigms and the potential of innovative treatment strategies and technologies need proper legal support through regulations that stimulate research, recognize the new realities and facilitate the implementation into health programs.

- Regulations on clinical research should be viewed for the benefit of the patient and allow adaptability to the research aims, such as risk-based approaches. Simplification of patients' information sheets is one example to reduce the barriers to more patient inclusion.
- The European Medicines Agency is enabling market approval by supporting medicine developers, exploring adaptive pathways to market, and contributes to the development of the regulatory environment; a further dialogue with all stakeholders is still needed, including trialists and patients, e.g. for trial design and GCP guidelines.
- ICT in health, and use of patient registries, biobank material and 'Big Data' may not be harnessed to full potential unless there is comprehensive discussion and regulation addressing all, sometimes conflicting, interests.[145]
- The regulatory framework needs integration to remove unnecessary complexity when needing to undertake health research, e.g. the regulations for clinical trials and data protection both pertain to health research; animal research and safety are both of importance for pre-clinical research. Harmonization at EU level and actors at national level is needed.
- For many novel treatments, the classic approaches for approval lack the necessary 'cross-border' pathways. This applies to mixed products, such as genetically modified stem cells and drug delivery systems. The European Medicines Agency only has authority in specific areas (medicines), whereas separate pathways for devices and their track for approval, in particular for novel technologies, hamper access by patients or may be insufficient to evaluate true benefit, e.g. for diagnostic modalities. The rules need to adapt to the technology and allow proper, yet fast, evaluation of 'disruptive' innovation.
- Harmonization of Health Technology Assessment is being addressed but still needs substantial work for integration across Europe. Research for HTA needs to be viewed within the overall health research framework.

6. ENSURING A LONG-TERM RESEARCH POLICY AND VISION THAT IS VALUE-BASED, HEALTH-AND PEOPLE-CENTRED, AND SCIENCE-LED

The final goal of research policy in the biomedical domain is better health, through knowledge and insight, translation and implementation. European values and a focus on health and well-being of every citizen must guide policy development.

A long-term perspective, continuity and strategic investments can unlock the potential generated by the recent achievements. Public health as the ultimate goal requires a holistic view, beyond coordination and harmonization.

The investment in and strategic priorities for biomedical and health research are decided in many fora along the innovation cycle. Public funding, which support the basic exploratory 'blue sky' research as well as early translation, is decided within the global finances budget and is interdependent with decisions in all other departments[146]. Research performing organizations, whether public or private, have internal strategies; academies set out recommendations. At EU level, alignment across directorates[147] (for example: research, health, IT) should include strategic research priorities. A broad stakeholders' forum and consultation on the research agenda should also include the public at large, patients and charitable organizations[148].

Implementation of a comprehensive policy requires action across sectors and involvement of the whole of society. "Health in all policies" has to become a priority in science, in the private sector, in policymaking, public bodies, and in civil society and should become a landmark for research in Europe. It is necessary to stimulate increased public engagement in the health debate at all levels and EU wide, finding new ways of active involvement of citizens in health information, services and research.

A more proactive policy and international commitment by Europe is urgent. It is particularly important to coordinate European programs with the national priorities of national governments in Europe to make a real difference at the global scale. Europe, Member States and the EU, should develop a comprehensive vision and action plan, setting out a strategy through consultation with all stakeholders.

Setting priorities requires a balance between addressing medical needs and building on opportunities, and must ensure excellence. Therefore research policy needs scientific leadership, continuity and broad consultation at a scale that takes full advantage of the European Research Area. The policy and related strategy should facilitate daring novel ideas, reaching across the innovation cycle; support collaborative, synergistic, and complementary activities in a joint enterprise between stakeholders and society.

The EU and Member States hold a unique position to further investigate the concept of a science-led European Health Research Council, or platform[149]. It could develop and support a global vision and research policy within the European context, and boost excellent research through enhanced cross-border collaboration, building on the success and potential in Europe.

The Scientific Panel for Health[150] is a pilot in such an approach, but a dedicated body for European Health Research is needed for a long term commitment to better research for better health for Europe.

Better research for better health needs

- a comprehensive policy for health research, defining common actions across EU and member states, including all actors

- implementation of 'health in all policies'

- a long-term mechanism to ensure the best strategies and highest quality in health research by a science-led multi-stakeholders' platform, including patients and society at large

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NOTES AND REFERENCES

[1] The terms "Europe" and "European" used throughout the document refer to the geographical entity and European Union Member States.

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[15] Other examples include: CreoDK, the joint research office of the University of Copenhagen, Technical University of Denmark, Copenhagen Business School and the Capital Region of Denmark (see their December 2014 document "Workshop on Implementation of Solutions in European Health Systems"); The European Federation of Pharmaceutical Industries and Associations (EFPIA) (see their 2014 document "Health & Growth. Working together for a healthy Europe: A vision towards a life sciences strategy for Europe); The Independent Expert Group on the Future of European Public Health Research (see their 2013 "report of the Independent Expert Group on the Future of European Public Health Research: Subgroup 2); and the World Health Organisation's Regional Office for Europe (see their document "Health 2020: A European policy framework and strategy for the 21st Century").

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[137] NordForsk is a joint funding initiative that facilitates and provides funding for collaborative national research between the Nordic countries (Denmark, Sweden, Finland, Norway and Iceland). It is commissioned under the Nordic council of ministers which is formed of national councils, universities and other research funding bodies. A minimum of three countries need to contribute funding to an initiative along with funding from NordForsk itself. An example of NordForsk initiatives includes the programme on Health and Welfare which focuses on solutions to societal and public health challenges. One part of this programme is the construction of joint Nordic registers and databases for research purposes, which was issued in 2014 (see www.nordforsk.org/en for more information).

[138] Article 185 is part of the Title of XIX of the Treaty on the Functioning of the EU (TFEU) dedicated to 'Research and technological development and space'. It allows the EU to conclude agreements with Member States, in order to participate in and support research and development of national programmes. The EU provides financial support to the joint implementation of the national research programmes involved, based on a joint programme and the setting-up of a Dedicated Implementation Structure (DIS). The DIS is the core recipient of EU funding in this type of initiative; it is responsible for the administrative, financial and contractual management of the joint research programme as well as the main point of contact for the European Commission. Examples of Article 185 initiatives include AAL (Active and Assisted Living Research and Development) and EDCTP2 (European and Developing Countries Clinical Trials Partnership Programme). The AAL138 aims at increasing the sustainability of care systems, by enhancing the availability of ICT based products and services for active and healthy aging. It is formed of a combination of private-public partnerships between companies, research institutes and the public sector across 17 countries. With accelerating innovative ICT based products, innovation and research at EU level in technologies can occur and a coherent European framework can be formed to develop common as well as localised solutions. The EDCTP2 (a continuation of EDCTP1) aims to reduce the social and economic burden of poverty related diseases in developing countries by accelerating the clinical development of medical interventions for poverty related diseases (see http://ec.europa.eu/research/era/art-185_en.htm for more information).

[139] The US' National Institute of Health (NIH) is formed of 27 different institutes and centres, where the majority receive funding from congress and administrate their own budgets. In 2015 NIH funded over 300,000 researchers at over 3,000 universities, medical schools and

other research institutions within the US as well as around the world. Examples of collaboration with Europe include the partnerships between NIH and Italian scientists in the development of a nasal test for human prion disease , and the partnership between the National Institute on Drug Abuse (NIDA) and the French scientific and technological institute focusing on human health (INSERM) in researching the neuroscience of addiction (see www.nih.gov for more information).

[140] Cancer Core Europe is a consortium of European cancer centres from the UK, France, Sweden, Netherlands, Spain and Germany. Formed in 2014 it aims to link cancer programmes on a huge scale to help the joint monitoring of patients and the development of next generation clinical trials, and will rival the American National Cancer Institute. Four areas of data are to be linked across the partnerships to create a virtual 'e-hospital' enabling joint research programmes: electronic medical records; molecular imaging and diagnostics; clinical trial infrastructure; and development of innovative new generation clinical trials (see http://www.cam.ac.uk/research/news/cancer-core-europe-institutes-unite-across-europe-to-tackle-cancer for more information).

[141] The National Institute for Health (NIHR) in the UK, aims to establish the NHS as an internationally recognised centre of research. It supports collaboration between the life sciences industry, charities, academia and the NHS. The NIHR is reviewed by an international panel of experts, where in 2015 six out of the 10 members were from European countries. An example of an international initiative funded by the NIHR is the study on the rare skin condition 'Xeroderma Pigmentosum', which includes 400 patients from five different countries (see http://www.guysandstthomas.nhs.uk/news-and-events/2015-news/october/20151015-skin-cancer-survivor-inspires-research-study.aspx for more information).

[142] Danish national public research and development funding can be used for cross border co-operation. Danish research programmes have a rule that nationality should not affect participation in Danish research programmes, but the research will only be funded if it aligns with Denmark's national priorities in the long term. For example there are bilateral research collaboration agreements with India, China, US, Japan and Israel, such as cross border contact between researchers and high tech firms (see https://ec.europa.eu/research/innovation-union/pdf/6-2_jorep_national_report_DENMARK.pdf and http://www.oecd.org/gov/regional-policy/publicationsdocuments/Oresund.pdf for more information).

[143] Imperial College London has a number of integrated healthcare partnerships to build innovation capacity within clinical research and practice and promote uptake and dissemination of new medical breakthroughs. The aim is to turn scientific discovery into better health for patients. Imperial has an Academic Health Science Centre (AHSC) and Academic Health Science Network (AHSN) that work together in promoting 'bench to bedside' healthcare. The AHSC focuses on discovery science and early stage translation and AHSN focuses on knowledge mobilisation and delivery of evidence based practice into healthcare. For example the NIHR Imperial Biomedical Research Centre (BRC) takes research findings from the laboratory into clinical applications to benefit patients. The BRC has set up an Imperial Centre for Patient Experience Research to rapidly transform research into evidence based initiatives for patients, which will work closely with the Imperial Clinical Trails unit as well (see https://www.imperial.ac.uk/medicine/partnership/healthcare/ and http://imperialbrc.org/our-impact/case-studies/patient-experience for more information)

[144] EIT health is one of the few current examples of this form of collaboration. It is one of the largest healthcare initiatives worldwide promoting healthier living and wellbeing of people across Europe. EIT focuses on cross-border interdisciplinary research between 140 leading organisations in healthcare, such as Pharma, MedTech, Payers, Research Institutions and Universities. Along with healthcare companies, EIT's core partners cross sector boundaries including CEA, a public organisation and leader in research in low-carbon energies, defence and security, information technologies for health, and, promoting the transfer from research to industry; ATOS Spain S.A., a leading company in digital services and business technology; and Achmea Insurance Company. (see http://eit.europa.eu/eit-community/eit-health for more information)

[145] The slow progress yet recent agreement of the Data Protection Regulation will be a major test case of whether the right balance has been found in the legal framework to support research and improve life. http://ec.europa.eu/justice/newsroom/data-protection/news/151221_en.htm.

[146] The European Fund for Strategic Investments (EFSI) is an initiative launched by the European Investment Bank (EIB) Group and the EU commission, which uses public funding to support private funding initiatives. More specifically, the aim is to help overcome the current investment gap in the EU by mobilising private funding for strategic investments. EFSI is one of the three pillars of the Investment Plan for Europe and has a EUR 16 billion guarantee from the EU budget and a EUR 5 billion allocation of the EIB capital. ESFI has its own governance structure in place and aims to support projects everywhere in Europe and in any sector; there are no geographic or sector quotas. Each project is reviewed on an individual basis for funding. With Horizon 2020, 3.5% of the budget for research and innovation will be transferred to the ESFI. This capital will enable ESFI to generate additional investments of EUR 315 billion (see http://europa.eu/rapid/press-release_MEMO-15-3223_en.htm for more information).

[147] An example of an EU complimentary research agenda can be seen in the EU Active and Healthy Ageing Initiative. The initiative is led by DG Connect with the focus on allowing people to age actively and independently with support from ICT based innovation. DG Connect is working with a range of partners including DG SANTE through EIP-AHA, DG EMPL (supporting their policy recommendations for long term care and targets in the Social Investment Package), DG REGIO (assisting regions to develop smart specialisation in health and ageing), DG EAC for EIT-KIC on Healthy Living and Active Ageing, and also with Member States on the Active and Assisted Living Joint Programme and on Joint Programming Initiative on More Years Better life (see https://ec.europa.eu/digital-agenda/en/policies-ageing-well-ict for more information).

[148] GlaxoSmithKline (GSK) is a good example of a public-private relationships working together to achieve a common goal. GSK regularly works with other UK and international funding agencies such as the Research Councils and third sector bodies, for example the Wellcome Trust, to leverage funding in areas of science where both sides have an interest. This is often done in a consortium arrangement with other companies in the life sciences sector. Public investments in patient data infrastructure are also thought to be an important area of future benefit for companies like GSK. For example, the further development of electronic patient health records could improve the UK's infrastructure for clinical research investment by the sector, leading to enhanced patient benefit through improved patient enrolment into clinical trials and better safety monitoring (pharmacovigilance). There was a sense that countries that were able to develop this data infrastructure successfully would see increased investment and collaboration from the private sector as a result. (see http://www.gsk.com for more information)

[149] The notion of a science-led body for European Health Research is increasingly being called for. Already in 2012 group of stakeholders gather with the Alliance for Biomedical Research in Europe and launched a call for a European Council for Health Research (http://www.biomedeurope.org/images/pdf/developments/Concept_Paper_EuCHR_Biomed_Alliance_FINAL.PDF). The Standing Committee of the EU Medical Research Councils (EMRC) for the European Science Foundation recommended to the EU parliament a new science led funding mechanism in the EU to support clinical or health research projects that require a multinational approach (http://www.esf.org/index.php?eID=tx_nawsecuredl&u=0&g=0&t=1456825874&hash=5c3334d1aa6954169162ff039e8eb7163d3ee603&file=fileadmin/be_user/research_areas/emrc/SRG-MED/2015/2012November_EMRCtoMEPs.pdf). Before that, in 2011, the European Medical Research Councils had called for a common EU science policy so that the EU will be able to 'influence global healthcare to improve human welfare and provide a better future for the EU, and its citizens and its industry' (http://www.esf.org/fileadmin/Public_documents/Publications/emrc_wpII.pdf).

A report published by the EU commission in 2013 by the Independent Expert Group on the Future of European Public Health Research, also identified the need for a board of public health research which would provide strategic direction to the entire field of EU public health

(http://ec.europa.eu/research/health/pdf/eu-h2020-subgroup2-report_en.pdf). This would be made up of a range of stakeholders including research associations, civil society, leading experts and public health institutions in MS. The tasks of the board would include identifying long term public needs and development research programmes and implementation of outcomes across all level of society in the EU.

Most recently, in 2014, the European Federation of Pharmaceutical Industries and Associations put forward a vision towards a life science strategy for Europe that called for a network of European Institutes of Health Research and Excellence to be established as a point of coordination for biomedical research (http://www.efpia.eu/mediaroom/170/44/At-the-heart-of-economic-growth-EFPIA-launches-groundbreaking-vision-towards-a-life-sciences-strategy-for-Europe). This network "should adopt a holistic and long term perspective on the health challenges facing Europe, foster public-private partnerships on open innovation within biomedical research, and champion regulatory reform to enable and reward innovation".

[150] https://ec.europa.eu/programmes/horizon2020/en/h2020-section/scientific-panel-health-sph