NFU priorities in health research

Dutch perspective in a European context
Preface

In presenting this position paper, we aim to contribute to the development of the new European research and innovation programmes that are due to get under way in 2014. We believe this is the right moment to come up with new ideas that can meet the health, demographic change and wellbeing challenge as formulated in Horizon2020.

In 2010 we began developing our initial thoughts on the new research and innovation programmes by identifying eight priorities that will make a significant contribution to tackling the societal health challenges ahead. We presented that first position paper to Commissioner for Public Health John Dalli and Commissioner for Research and Innovation Máire Geoghegan-Quinn. This new position paper contains a further elaboration on the priorities identified in 2010.

What's new? In the intervening period, we have taken full account of the recently published approach in the context of the European Innovation Partnership on Active and Healthy Ageing. This approach also corresponds with the Dutch government's Topsector policy, which aims to boost the innovation climate through the creation of and collaboration in public-private partnerships. You are cordially invited to read about these new ideas, suggestions and remarks on how to address the major societal challenge of health, demographic change and wellbeing.

The present position paper is a collaborative effort by the Netherlands' eight University Medical Centers united in the Federation of University Medical Centers (NFU), a large number of scientific experts working in research and innovation at these Centers and The Netherlands Organisation for Health Research and Development (ZonMw). Our strength in these fields gives us the confidence that we will be able to make a highly valuable...
contribution to future EU initiatives in the field of health. The position paper reflects the goals of Horizon2020, the European Innovation Partnership pilot Active and Healthy Ageing, and the relevant Joint Programming Initiatives.

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Executive summary

Contribution of NFU research and innovation themes to the European grand societal challenge

In 2010, the NFU and ZonMw\(^1\) engaged in a process to design a vision and a research agenda to address challenges in health research for Europe. Here, the NFU presents the prioritized five disease and enabling technology focused topics, and three research infrastructural themes for the European research agenda in more detail. The prioritized themes presented are identified to tackle the grand societal challenge of health, demographic change and wellbeing. Together the themes form a coherent and complementary agenda, in which prevention and intervention are well balanced. In addition, the specific topics per priority may contribute to the Dutch agenda of medical research for the EIP on Active and Healthy Ageing to leverage EU and national research and innovation programmes.

- Improving health in an ageing population
- Neurodegenerative diseases
- Metabolic syndrome and obesity
- Regenerative medicine
- Collective action for health improvement
- Biobanking
- BioImaging
- Clinical research

The NFU and Horizon 2020

The themes were selected in view of the societal challenge of an ageing population and its impact on changing societies. The NFU vision builds on the further integration of (European) research, innovation and regional policies. Therefore it is essential to view Dutch strengths in health research against a background of complementarities present in other Member State, and to further investigate options for true collaboration and harmonization of efforts, such as in Joint Programming Initiatives. The aim of this process is to enhance efficiency, and eventually accelerate the
transfer of knowledge, innovation in health products and services, and the actual deployment in healthcare in order for European patients and citizens to benefit faster, while stimulating European competitiveness at the same time. This vision is in line with the three goals of Horizon 2020:
1) Excellent science
2) Industrial leadership
3) Societal challenges
Executive summary

**UMCs in international networks**
The NFU represents the eight University Medical Centers in the Netherlands. The UMCs integrate medical education, (bio)medical research & innovation and patient/health care functions. UMCs combine smart specialisation in highly specific areas, with excellent basic research, when possible coupled to regionally clustered innovative industry, and/or health and welfare service chains (3D-model of Discover, Design and Deploy). They collaborate in international, national and regional networks. All three levels include a substantial number of public-private partnerships, in line with Dutch policy.

**The NFU and the EIP on Active and Healthy Ageing**
In June 2011, the NFU has announced a Dutch research agenda for active and healthy ageing. This NFU vision and agenda also specifically addresses healthy ageing with a life course approach. It focuses on medical priorities, technology for assisted living, and food and nutrition in connection with health, showing the intricate relationship between these sectors under theme 1. However, the other themes are crucial for healthy ageing as well, such as prevention and public health in theme 5 and neurodegenerative diseases in theme 2.

The NFU and ZonMw are convinced this research agenda will help shape Europe’s response to a number of major global challenges in the decade to come.

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1 *The NFU is the Dutch Federation of University Medical Centers (www.nfu.nl). ZonMw is the Netherlands Organisation for Health Research and Development (www.zonmw.nl), coordinating JPI in the Netherlands.*
Netherlands Federation of university medical centers
in cooperation with ZonMw

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This is a product of the NFU-committee international research:
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In 2010, the NFU, the representative of the Netherlands University Medical Centers (UMCs), took a first step in strategic research agenda setting at a European level to tackle major societal questions. The first position paper “European priorities in health research, a Dutch perspective” was discussed with and presented to members and representatives of the European Commission and the European Parliament on April 15th 2010 at an invitational seminar in Brussels. Here we present the extended vision and research agenda of the NFU and ZonMw on the added value of Dutch medical and health research towards the development of the European research agenda. The NFU does so in view of:

- The grand societal challenge of health, demographic change and wellbeing
- The implementation of the EU2020 strategy, Horizon 2020, the Innovation Union, the European Research Area (ERA) and the European Innovation Partnerships (EIP’s).

The NFU vision builds on the further integration of (European) research, innovation and regional policies, and the concomitant funding instruments (Horizon 2020 and European Regional Development Fund). This is envisioned as a smarter way to support researchers and innovators in Europe – so as to

1) tackling Societal Challenges,
2) boosting Industrial leadership, and
3) raising Excellent Science.

The NFU and ZonMw acknowledge their role and responsibility in the process of building a health research and innovation system in which regional-, national- and European-level processes interact in a coherent and optimal fashion.

UMCs fulfill a central role in the health value chain. They do not operate in isolation, but collaborate in international, national and regional networks, (public-private) partnerships and consortia. The ever-increasing complexity and specificity of innovations requires
input from multi-disciplinary partners and sectors. Efficient collaboration in partnerships increases the output and valorisation potential. The Dutch UMCs have been active participants in the European programmes and highly value future participation. The UMCs also want to act ‘small’. Smart specialisation in highly specific areas, with excellent basic research, when possible coupled to regionally clustered innovative industry, and/or health and welfare service chains. In the future even more clustering of research and innovation activities will take place.

It is key to view Dutch strengths in health research (infrastructures) against a background of complementarities to other Member State or regional research bases, and to further investigate options for true collaboration and harmonization of efforts. The aim of this process is to enhance efficiency, and eventually accelerate the transfer of knowledge, innovation in health products and services, and the actual deployment in healthcare in order for European patients and citizens to benefit faster, while stimulating European competitiveness at the same time. Experiences with pooling Member State resources (e.g. through the first steps towards Joint Programming Initiatives) have demonstrated the potential impact and efficiencies offered by leveraging other public sources of funding. Therefore, national activities to create synergy and developing European strategic research agenda's are addressed in this position paper as well.

The NFU and ZonMw
In health research, the eight Dutch UMCs act as one, the NFU being their patron and spokesman in the Netherlands and Europe. Essentially, the Dutch UMCs combine several roles. By merging the Faculty of Medicine with the university hospital into UMCs, the UMCs have positioned themselves at the intersection of medical education, (bio)medical research, and patient care. UMCs integrate teaching, research&innovation and health care functions, bridging the gap between generating, translating and applying knowledge.
ZonMw, the Netherlands Organisation for Health Research and Development, is building on the same principles as the UMC’s; connecting basic research and implementation in practice on the shortest route possible. ZonMw is also a main player in international collaboration and
coordination of health research: it facilitates the Dutch contribution to European initiatives on behalf of health policy, research and practice. E.g. ZonMw is heavily involved in a number of Joint Programming Initiatives, it represents the Netherlands in various international committees, exploring the possibilities of international cooperation on specific themes or subjects. ZonMw endorses the NFU European agenda.

The new Dutch industrial policy stimulates competitiveness by creating favourable framework conditions for the life sciences, agro-food and technology industry to flourish in the future, and aims to be aligned with European policy.

**Thematic priorities**

Europe’s response to a number of major global challenges will shape its future in the decades to come. In the health sector, a real contribution to the needs and demands of the European citizens can be achieved. Therefore the NFU prioritized in 2010 the following five disease and technology focused topics, and three research infrastructural themes on the European research agenda (see also figure).

- Improving health in an ageing population
- Neurodegenerative diseases,
- Metabolic syndrome and obesity,
- Regenerative medicine
- Collective action for health improvement
- Biobanking;
- Biomedical Imaging;
- Clinical research.

**GRAND CHALLENGES EU**

**Dutch contribution NFU**

Healthy ageing

Preserving health

- Improving health in an ageing population
- Neurodegenerative diseases
- Metabolic syndrome and obesity
- Regenerative medicine
- Collective action for health improvement
- Biobanking;
- Biomedical Imaging;
- Clinical research (incl. translational research)
Here, these eight themes have been further elaborated to contribute relevant topics to the European strategic research agenda. These topics help starting to create European networks and search for partners in European Member States to work together where possible and necessary. For each theme a vision is presented of how research contributes to solving societal challenges; subsequently specific priorities for the European strategic research agenda are described in some detail. Each theme concludes with a summary of theme specific EU and national networks.

For each theme the topics on the strategic research agenda try to strike a balance between priorities in scientific excellence (‘discovery’), innovation (‘design’), and implementation (‘deploy’). Not every topic though has matured so much that actual deployment is feasible on the shorter term, and not every topic will benefit equally from European collaboration. Thus, a further inventory of other Member State strengths and complementarities will help in further alignment and focus per topic.

The creation and maintenance of world-class research infrastructures in Europe is crucial. Both European Commission and the Member states need to take the lead in establishing research infrastructures by development of and investment in pan-European research infrastructures. The NFU has committed itself to biobanking, bioimaging and clinical research infrastructures because of their intricate links with the disease themes, and because UMCs are excellent workplaces for these infrastructures.

**The EIP on active and healthy ageing**

The start of the pilot European Innovation Partnership (EIP) on active and healthy ageing has brought together a wide range of stakeholders, and it has delivered a shared, comprehensive framework for action to promote active and healthy ageing in Europe. The new paradigm is that ageing is considered an opportunity rather than a burden, valuing older people and their contribution to society; and seeking to empower them through user-centred innovation and service delivery. There is a holistic and multidisciplinary focus on services and products for the elderly people,
which contribute to sustainable care systems of tomorrow. Value to older people should go hand in hand with delivery of long-run budgetary savings. The EIP aims to increase by 2 the average number of healthy life years in the EU by 2020. Therefore, it has structured the work in three pillars:
- Prevention, screening and early diagnosis
- Care and cure
- Active ageing and independent living

In June 2011, the NFU has announced a Dutch research agenda for active and healthy ageing. In this position paper the NFU redeems its promise: the medical research agenda for healthy ageing is presented under theme 1, addressing topics that are relevant for the age group of 55-70 years. Prevention and public health related to ageing is addressed in theme 5, collective action for health improvement. In theme 2, an elaborated research agenda on neurodegenerative diseases contributes to the problem of cognitive impairment in elderly people, and likewise, the other themes all have elements that are (in part) relevant for the EIP on active and healthy ageing. At the same time, the themes contain extensive agenda setting for Joint Programming Initiatives (JPI) such as the JPI on Neurodegenerative diseases, and JPI More Years, better lives, in which Member States have to join forces, and strategically share resources. In addition, the research infrastructures have intrinsic infrastructural impact for all medical research, and are beneficial to all the medical and technology oriented themes. Because active and healthy ageing extends beyond a medical perspective and includes social, labor market and ICT-aspects as well, a wider consultation of stakeholders is needed to finalize a comprehensive Dutch research agenda on active and healthy ageing.

The prioritized themes presented here are identified to tackle the grand societal challenge of health, demographic change and wellbeing. Together they form a coherent and complementary agenda, in which prevention and intervention are well balanced. In addition, the specific topics per priority may contribute to the Dutch agenda of medical research for the EIP on Active and Healthy Ageing.
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The UMCs: discovery, design and deploy

Here, the NFU presents the Dutch experience with stimulating innovation in University Medical Centers. UMCs provide an excellent workplace to combine scientific excellence, directly addressing societal challenges through their contact with end-users, and collaboration in public private consortia to support competitiveness.

Essentially, in a UMC all phases of generating and translating knowledge do take place, and the NFU stresses the importance of paying equal attention to all these phases. The figure shows how the Dutch University Medical Centers integrate the various phases and national and international players in the knowledge, innovation and healthcare chain. The so-called 3-D model complies with the goals of the Innovation Union, Horizon 2020 and the EIP on active and healthy ageing.

**1D Discovery – Excellent science**

The Discovery phase, with a major contribution from bottom up, curiosity driven research, is essential to fill the innovation pipelines. The UMCs participate in a large number of projects in the current and previous Framework Programmes (Cooperation, Health). They contribute to basic science, both in national and EU-wide collaboration, as shown from the general high position in publication and citation rankings. In addition, the UMC’s play a leading role in building research infrastructures in the biomedical sciences and have taken their responsibility in EU research infrastructures. And in order to optimize alignment with future and emerging technologies (FET), systematic alignment and collaboration with the three Dutch Technical Universities (3TU) has been guaranteed. The Discovery phase links directly to the Horizon 2020 efforts to create excellence in the science base.
The UMCs: discovery, design and deploy

2D Design – Industrial leadership
The Design phase, in which best practices or new products and services can be further developed, needs more attention, especially when transition fails or is hindered by unfavorable preconditions. Involvement of all relevant stakeholders is needed to create a favorable innovation climate. The UMC’s are all participating heavily in the public-private partnerships (Top institutes) in the Netherlands. These Top institutes address challenges in translational molecular medicine (CTMM), in biomedical materials (BMM), in food and nutrition (TIFN), innovative medical devices (IMDI) and in pharmaceuticals (TIP) and play a key role in the build- bundle-benefit strategy to stimulate industrial activity and support SME’s. Currently, these top institutes together with the enabling technologies and infrastructure clusters are part of the Dutch Top Sector plan Life Sciences, and cross-sectoral with the Agro-Food and Technology sectors. In the Top Institutes, UMC’s collaborate directly with both big industrial partners, and with innovative SME’s. The Design Phase links directly to the Horizon 2020 efforts to strengthen industrial leadership and the competitiveness framework.

3D Deploy – Societal challenges
The demand for healthcare solutions is growing and changing. This coincides with increasing pressure on supply from a shrinking workforce and rising cost. Medical innovations, therefore, must not only make people better, but also save work and help contain costs. The transition to successfully generate, translate and deliver a continuous stream of innovations to patients, - or entering the deploy phase - includes involvement of early adopters among the end-users to ensure successful implementation and added value for the European citizens. The UMC’s have direct access to end-users and are able to interact with them and investigate innovative and state of the art treatments. European collaboration is necessary to harmonize, standardize and evaluate such diagnosis, cure, care and prevention products and services. Regional expertise centers for specific treatment can be beneficial for patients and citizens.
**Societal and economic benefit**

Robust attention for Discovery and Design is a prerequisite for Deployment: so building and maintaining a set of strong, sustainable pipelines in chosen areas of focus and supporting these with a enabling technology and infrastructure, will create health and wealth. In order to facilitate each phase and to connect the three phases, appropriate infrastructure is needed.

UMCs fulfill a central role in the health value chain; they do not operate in isolation. Extensive national and international collaboration takes place in networks, (public-private) partnerships and consortia. In these consortia, end-users (patients and citizens), health organizations, charities, health insurers – in other words – the people are the true beneficiaries of addressing grand societal challenges.

The NFU is convinced that to achieve the 3D ecosystem, it needs to operate in a European context. This is necessary to deal with the ever-increasing complexity and specificity of innovations. Input from multiple partners is essential and new forms of multilevel governance (transnational, public/private, global) are needed.

Therefore, added value of this position paper is:

- Contributing to agenda setting of Horizon 2020, and the EIP on active and healthy ageing;
- Setting the stage for alignment with current European initiatives, including international bodies and networks;
- Setting the stage for further strategic alignment with partners in other Member States, to increase efficiency of resources and;

**The NFU and ZonMw are convinced this research agenda will help shape Europe’s response to a number of major global challenges in the decade to come.**
Theme 1: Improving health in an ageing population

Vision

Ageing is one of the grand societal challenges of the forthcoming decades. An ageing population in fact represents several challenges, one directly ensuing from the general health of older adults, which is characterised by increasing multi-morbidity. Another arises from diminishing performance at work and in society, which among others directly affects the sustainability of our health care systems. The oldest age-group (aged > 85 years) is rapidly expanding. This group is clearly prone to develop disease and disabilities. On the other hand pension benefits and labour shortage will in the near future dictate reassessment of the role of the population aged between 55 and 70 years. A continued contribution to the gross domestic product and society at large is warranted. Apparently, a considerable part of the European strategy and research and innovation efforts will focus on the potential gains among residents aged 55 and 70 (i.e., reduction of health care costs, maintenance or increase of productivity, and quality of life).

Indisputably, relevant innovations will emerge from such focus. However, vast opportunities may be lost should not younger age-groups/generations be included: healthy ageing begins at, or even before, conception. Parents pass along their genes, accompanied by exposures and risks that can lead to a healthy life course or conversely the development of illnesses and loss of function later in life. Environmental factors, nutritional patterns, stressful experience, other life style characteristics, such as the amount of exercise and smoking habits, and the use of medication are all factors that affect the development of health. In addition, early identification of those at increased risk of (multi)morbidity, impaired quality of life and social functioning later in life is crucial to target effective interventions. The influence and interplay of causal factors related to functioning in later life and the optimal way to efficiently predict the latter remains to be established. Therefore, new knowledge is needed.
Topics for the EU research and innovation agenda
In accordance with an integrated healthy ageing strategy the NFU/ ZonMw recommends the following research priorities. These priorities take healthy ageing with a life course approach focussing on medical, nutrition and technological aspects; prevention and public health are addressed in NFU-topic 5, collective action for health improvement. Together with the healthy ageing related priorities in the other NFU topics, they contribute to the Dutch national agenda for The EIP of Active and healthy Ageing. The priorities address all aspects of the research and innovation cycle: discovery (insights from science), design (best practices, new products or technology) and deploy (implementation in society).

1. Strengthen the knowledge of the ageing process
Essentially, this topic, and its four sub-topics are starting with curiosity-driven research (‘discovery’). The Netherlands has a leading position in research into the underlying biological mechanisms of the ageing process, and Dutch initiatives have secured the connection to deploy the new knowledge in clinical practice. Europe may provide complementary knowledge here, e.g. in animal models. At the same time, these sub priorities address needs that pose a great burden on health, the care system, the health care budget and society at large. While having a strong discovery oriented focus, this type of research is largely demand-driven. The subtopics are:
- More basic research to unravel ever active and underlying biological mechanisms of the ageing process, and how to influence this process.
- More basic research to unravel the underlying mechanisms of several concurrent age associated diseases (multimorbidity) like chronic low-grade inflammation, insulin resistance, growth hormone action et cetera.
- Research is needed aimed at the interaction of mental and physical health. Besides having a major impact on quality of life, common mental disorders such as anxiety, depression and somatoform disorders also mark an increased risk of future physical health problems and aggravate disabilities associated with these somatic problems. Mental health is thus not only in itself but also because of its interactions with physical health of crucial importance for healthy ageing. These types of problems
can be tackled by medical (disease-oriented) approaches or functional (behaviour-oriented) approaches.

- Research into the last (‘fourth’) stage of life: old age comes with syndrome-like features of declining function. These syndrome-like features represent the diverse so-called ‘geriatric giants’: immobility, instability, incontinence and impaired intellect/memory. Health issues in older adults may also include long-term care, burden of caregivers, social participation, falls, delirium, use of multiple medications, mental problems such as anxiety and depression, impaired vision and hearing. The combination of these problems renders individuals’ frail and complex, i.e., only a slight further decrease in any given function may tip the balance and these already high demanding individuals become completely care dependent.

2. Develop new tools and strategies for prevention of disease and loss of function

This topic, and its six sub-topic, needs pan-European attention and support, since little tools for prevention and loss of function are available as yet. It requires a visionary and integrated approach to address the whole value chain, in which European partnerships provide added value. It holds for personalised medicine, for tools and for services, and all six subtopics are all relevant for the strategic research agenda of the EIP on Active and Healthy Ageing. From an implementation perspective (deploy), collaboration with healthcare organisations is key. Likewise, from a prevention perspective, close connection with NFU-topic 5; collective action for health improvement is crucial to define effective strategies in practice. From a business perspective, there is Dutch strength in medical technology designed for the elderly. In this area of translational research the contribution of large industry, SMEs, academic research groups and especially private-public partnerships are essential. The subtopics are:

- Translation of basic knowledge into evidence based and life-long personalised medicine.
- Development of new tools and strategies for prevention of disease and disability and to maintain functional autonomy in older age. This includes intervention methods to be adopted by health care professionals (e.g. nurses, physicians) to strengthen (rest)capabilities and to improve
Theme 1 - Improving health in an ageing population

- Development of medical technologies, services and care innovations for personalised health care systems for frail individuals, e.g., cancer survivors and many of older persons. This includes for example enabling technologies for regenerative medicine.
- Test treatments that are specifically focussed on the pathophysiology of aging, such as polypills addressing multimorbidity, exercise combined with drug prescription, and drugs or non-drug interventions that address the damage accumulation of aging.
- Development of novel strategies to identify individuals (both at an older age and at younger ages) at increased risk of impaired functioning and multi-morbidity in later life, with the aim to target effective preventive interventions timely and at those most likely to benefit. Early potential predictors may be both causal and non-causal and include serum markers, point-of-care-tests, imaging techniques, “omics” parameters as well as short questionnaires.
- Develop instruments and technology that helps to lessen the burden of iatrogenic damage to elderly patients, which is still a major threat for our societies, because large-scale health care delivery is not adapted to the frailty and multi-morbidity of the older populations. Innovative systems of individualized repeated outcome measuring; benchmarking within and across medical specialities, and smart dashboards of safety and quality indicators may result in major gains of adding life to years and in major economic savings.

3. Active participation in society
This topic, and its five sub-topics, is mainly societal demand driven, and practical use of results is evident. While the actual societal needs are clear, research topics reach further than medical aspects only, as it addresses also work-live balance, healthy diet, physical activity and e-health system. Public authorities have a role in supporting targeted populations, notably the youngest and eldest age groups in our society. Industry and businesses can develop products and services that suit the needs of the intended consumers. As the share of elderly is growing, their
Market potential is increasingly being recognised. However, industry cannot be solely in the lead, because of the risk that their research and development may yield an un-pragmatic technology push. Uptake of new technologies by citizens and/or professionals might constitute a major hurdle. Therefore, end-user involvement and education is essential to create awareness and enable citizens to make healthy choices in daily life. The subtopics are:

- **Healthy ageing at work**: an (rapidly) ageing population is characterised by an increasingly unfavourable ratio between occupationally active and inactive people. Moreover, an ageing workforce generates new concerns about health and productivity in this population. In the Netherlands labour market participation of people aged 55 to 65 years is below 50%. For other European countries even lower percentages have been reported. More than half of the workers report difficulties in work performance due to health and age-related problems. A large part of these difficulties arise due to mental health problems, or physical health problems with a psychological component. Also, being carers for their older parents cause this kind of difficulties at work.

- **Medical and care technology and e-health applications to support ambient assisted living and functional autonomy**: Medical technologies and e-health represent great potential, for example by assisting older persons in their daily routine and support in health monitoring, also by involving the carers of the elderly, thus contributing to longer healthy and independent living. In addition, this also may help to resolve labour capacity shortages in the system for health care to older persons in the near future.

- **Enabling healthy choices**: together with companies and (inter)national research partners, the challenge lies in creating a safe and stimulating working environment that also encourages and enables people to make ‘healthy’ choices, i.e., that would result in a healthy and social active life. Research into balancing energy intake and expenditure, physical activity (mobility and sports) and how stress affects one’s ability to participate in society is needed.

- **Research and innovation strategies to enhance and support the uptake of new technologies**: As expectations and routines may differ across generations, social economic status, ethnicity and education, dedicated
research efforts are foreseen.
- Developing and comparing strategies by which older persons are actively involved in setting the research agenda and guiding research projects. So far running research projects and implementing research results is often hampered by barriers of recruitment and implementation. Smart and evidence-based participation models could make research efforts more effective and efficient.

Rationale for these priorities in EU context

The European Innovation Partnership on Active and Healthy Ageing (IP AHA) is a flagship initiative for the Innovation Union. This initiative is complemented by the Joint Programming Initiative ‘More Years, Better Lives’, in which healthy ageing is prioritized as well. In addition, two of the six Knowledge and Innovation Communities (KIC), that will be part of the European Institute for Technology (EIT), focus on ageing and innovations for healthy living. With the above priorities, the NFU intends to bring more synergy between research, innovation, education and regional funding with the aim to accelerate the transfer of knowledge into products and services that are beneficial for EU patients and citizens at large. In addition, the NFU presents the same priorities to all initiatives in order to avoid fragmentation and duplication. To support a multidisciplinary approach on concurrent age-related diseases, the NFU/ZonMw takes the point of view that a pan-European research infrastructure on basic ageing research would have added value.

In order to further create synergy, the NFU is aware of the fact that the UMCs can share their expertise not only with the EC, but also directly with other Member states. The Dutch strength is in the best practices that we can contribute to Europe. For some of the priorities the UMCs have a leading position in Europe, e.g. in genomics research into ageing (e.g. the Netherlands Consortium for Healthy Ageing (NCHA)), in which four UMCs collaborate with big industrial partners such as Philips, Unilever, DSM. For other priorities, collaboration in consortia between public research & innovation organisations and health or patient organisations has started (e.g. national program Care for Elderly (NPO) and the Netherlands Institute for Healthy and Successful Ageing (Ti-GO)). Two regional initiatives connect to European policy as well: one is the Medical Delta having a focus on
e-health and other medical & care technology applications, which fits into the EU e-Health Action Plan (2012-2020). And the other is the European Research Institute on the Biology of Ageing (UMCG/RUG) & the healthy ageing campus in Groningen, including a prospective biobank on ageing, which fits as a whole into the IP AHA. Biobanking is a stronghold as well in all UMCs, with specific sample collection for ageing related disorders such as neurodegenerative diseases, diabetes and CVA. All these consortia are learning how the value chain can benefit from an integrated approach, and most of them are actively internationally collaborating. ZonMw is actively involved in strategic agenda setting for the EIP in AHA, and this process could benefit from ZonMw’s involvement in JPIs in demographic change, neurodegenerative disease (JPND), and in Health, food and prevention of diet related diseases, which are all relevant for ageing as well. ZonMw and the NFU are both acting as linking pin to Dutch public authorities, thereby securing national an international policy. All together, the NFU priorities in this theme are well adjusted to future EC initiatives; they are balanced in discovery, design and deploy, responding to a strong societal need. Further collaboration with other member states in this area could be of added value, and requires further ‘end-user’ involvement.
Theme 1 - Improving health in an ageing population

Netherlands Federation of university medical centers in cooperation with ZonMw

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Theme 2: Neurodegenerative diseases

Vision

Neurodegeneration with resulting cognitive deterioration and ultimately dementia is one of the most important causes of disability of the elderly. It has a high impact on quality of life, health care resources and societal costs. Currently, more than 10 million people are diagnosed with dementia in Europe, and this number is expected to double by 2040 due to the increase of subjects of 80 years and older. Among the neurodegenerative disorders, Alzheimer’s disease is the most common cause of dementia accounting for up to 75% of the cases. Other frequent causes are vascular disease, Parkinson’s disease, Lewy body dementia, and frontal temporal lobe dementia.

The key towards prevention of neurodegenerative disorders is research. Although major advances have been made in the understanding of neurodegeneration, the pathophysiology is still not yet fully understood and treatment that can prevent or slow down neurodegeneration is lacking. Collaborative research is needed on all key domains of pathophysiology, animal models, genetics, diagnosis, prevention, therapy, and care organisation. There is an urgent need to understand the mechanisms of the disease better to develop effective treatment, and to develop prevention strategies or any intervention that leads to the delay of dementia. Eventually, new prevention and intervention strategies for neurodegenerative diseases may help to address the challenges that ageing poses to European citizens and society at large.

Topics for the EU research and innovation agenda

In accordance with an integrated strategy to respond to the societal challenge of health, demographic change and wellbeing, the NFU/ZonMw recommends the following research priorities. The neurodegenerative disease theme primarily focuses on treating and understanding disease, and not maintaining health, which is addressed in the theme on healthy ageing. The priorities are mainly oriented on early diagnosis, biomarkers for differentiation, and
specific intervention and prevention research, with a specific focus on translational studies into pathophysiological mechanisms. The public health side of neurodegenerative disease are addressed in NFU-topic 5, collective action for health improvement. The priorities are all designed from ‘bed to bench’, rather than from ‘bench to bed’. Hence, these topics are mainly societal, ‘deployment’ driven, and would ideally result in best practices that industry can take on.

1. Diagnosis and differentiation: design of biomarkers
Large cohort studies are needed to be able to identify the contribution of multiple genes in the onset and progression of neurodegenerative diseases. The multifactorial nature of these disorders requires European collaboration; hence the sub priorities below. Collaboration with industry should be pursued, but in the meantime UMCs are the working place where patients and researchers meet. The subtopics are:

- Cohort study of people with early onset dementia. Early-onset dementia is relatively rare. It has a strong genetic background. Studies on early-onset dementia provide the opportunity to clarify the genetic basis of neurodegeneration. Identification of carriers of autosomal mutations that cause neurodegeneration allows studying the development of the disease in the earliest stage. In addition, these subjects will be excellent candidates for studies in which new disease modifying treatments can be tested.

- Endophenotypes of Alzheimer’s disease and related disorders. Alzheimer’s disease and related disorders are characterised by a large heterogeneity in clinical presentation and progression. This suggests that Alzheimer’s disease and related disorders are not single disease entities but a group of disorders. Biomarker and genetic studies are needed to disentangle the different endophenotypes. This will be important to develop therapeutic strategies.

- Resilience to neurodegeneration. A small group of elderly subjects never develop neurodegenerative disorders. Moreover, a large group of elderly subjects have neurodegenerative changes in the brain but never develop cognitive impairments. Unravelling the clinical, genetic, and biomarker characteristics of these subjects may help to develop preventive strategies for neurodegeneration.
- Neurodegeneration in the oldest-old. Studies on neurodegeneration have typically been performed in subjects younger than 85 years. However, dementia is most common in the oldest-old. Neurodegeneration in the oldest-old differs from that in younger subjects. Pathology is more often mixed, the genetic background may be different, and the oldest-old have specific care needs. Studies are needed to define the genetic and biomarkers characteristics of neurodegeneration and care needs in the oldest-old.

2. Pan-European intervention studies: supporting the evidence base

From a deploy perspective, large diagnostic, prognostic and therapeutic intervention studies are needed, that build upon European infrastructures in biobanking, imaging and clinical research. In addition, connection to other themes is being made through further assessment of other life style factor related multifactorial diseases, such as cardiovascular diseases, and diabetes. The contribution of patient organisations, and health organisations is key to be able to organise and coordinate sufficiently large European cohorts. The subtopics are:

- Establishing the natural history of Alzheimer’s disease. Alzheimer pathology starts already 20 years before subjects become demented. The trajectory from the earliest pathological abnormalities to full-blown dementia is not well understood. Large long-term prospective cohort studies are needed to monitor changes in biomarkers and cognitive markers over time in subjects from age 50 onwards. This will provide insights in the development of the disease and will give clues for the development of early interventions and of diagnostic and prognostic markers. Studies should have a long-term follow-up and apply a multimodality approach incorporating genotyping, DNA expression profiling, biomarker analysis in blood and CSF, functional imaging techniques (EG, MEG, resting state f-MRI), MRI diffusion tract imaging, PET imaging, and structural imaging.

- Multifactorial road of cumulative damage. In elderly subjects dementia has often multiple causes. This concept of mixed dementia is not well understood yet but has important implication for the prognosis and therapy of patients. Innovative biomarkers are needed to disentangle the mixed burden of Alzheimer’s and vascular disease. Unbiased
Theme 2 - Neurodegenerative diseases

clinicopathological studies in older populations are needed to establish the relation between these biomarkers obtained in living subjects and the brain abnormalities after death. A joint effort in brain banking should be considered here. The study is of ultimate importance to reach evidence-based practice in diagnostics.

- Executing a pan-European intervention study in the pathophysiology of late-onset dementia. Lifestyle factors such as diet and physical exercise, but also modifiable vascular risk factors such as hypertension and diabetes mellitus play an important role in the development of late-onset dementia. Large-scale prevention trials are needed to establish whether modification of these lifestyle factors reduce dementia risk.

Rationale for these priorities in EU context

For these topics and subtopics, multidisciplinary consortia are needed including academia, companies on diagnostics and therapeutics, and patient organisations such as Alzheimer Europe. Within academia, collaborations are needed between clinicians, geneticists, biochemists, neuropathologists, and epidemiologists. Where possible, consortia should make use of existing infrastructure including clinical and population cohorts, ongoing clinical trials, biobank facilities, and imaging facilities. In order to reduce fragmentation, to prevent duplication, and to achieve critical mass, it is considered of crucial importance that within the Horizon 2020 programme national and European initiatives on neurodegenerative research funding are aligned. The first step was taken by the approval of Neurodegenerative diseases and Alzheimer as the pilot project for Joint Programming (JPND). Therefore, the priorities above contribute to the strategic research agenda setting that is taking place in the context of JPND. ZonMw is committed to JPND as member of the steering committee and as work package leader for a monitoring & evaluation framework. Next to dedicated calls to specific topics, it is suggested to allow open calls in which proposals are selected based on innovation and quality only. In addition, it is recommended to stimulate horizontal programmes on neurodegeneration across the different Directorates-General (Research and Innovation, Health and Consumers, Information Society and Media) and to further build upon a fully functional network of European centres of excellence working in the field of Alzheimer’s disease primarily, the
European Alzheimer's Disease Consortium (EADC). Dutch researchers are taking their responsibility in these European activities, eg in steering committees. More specifically, the Dutch consortia active in neurodegenerative disease are building their research on specific cohorts (biobanks), and they have a good track record in the area. The added value for Europe is to bundle these cohort studies with those of other Member States. Dutch research could also benefit from connecting with basic research groups on neurodegenerative diseases. To this end, further exploration of international projects such as DESCRIPA and EDAR is key; in these projects the main Neurodegenerative disease researchers' from European Member States are present. Further synergy can be created by connecting with research infrastructure initiatives for biobanking and for imaging. With BBMRI-NL and BBMRI-EU alignment is well established (via String of Pearls); more interaction with Eurobioimaging is relevant because of the impact of the use of imaging modalities on healthcare systems; at a national level, connecting Alzheimer and imaging is realised in the public-private partnership project LeARN (Leiden – Alzheimer Research Nederland) in which big industry and SMEs works together. Finally, while research is designed from bed to bench, stronger involvement of patient organisations should be encouraged in all stages of research and implementation.
Netherlands Federation of university medical centers
in cooperation with ZonMw

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Theme 3: The metabolic syndrome and obesity

Vision

Governments across Europe have recognized obesity and the metabolic syndrome as one of Europe’s most pressing public health challenges, particularly for children. They constitute a major threat to human well being and economy in Western society. It is expected that by 2030, about 33% of the total population in the EU-27 will be obese, and many of them will suffer from one or more co-morbidities. Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases, and cancer, which are all age-related diseases as well. Although obesity used to be a typical problem in the developed world, it has now become an issue in low- and middle-income countries as well, particularly in urban settings. Both obesity and metabolic syndrome have crucial effects on (labour) productivity and social participation. The cost of obesity has already reached 5% of public health expenditure in several European countries. And in an ageing population, these costs are expected to grow. The EU can play an important role in dealing with the grand challenge of preserving health through its public health and research policies. The metabolic syndrome is a cluster of conditions such as increased blood pressure, elevated insulin levels, excess body fat around the waist or abnormal cholesterol levels. This condition leads to an increased risk of developing cardiovascular disease and diabetes. In the past 10 years there has been considerable progress in developing technologies, collecting data and generating information on different aspects of the metabolic syndrome. However, our understanding of this disorder is still remarkably limited.

Topics for the EU research and innovation agenda

In accordance with an integrated strategy to respond to the societal challenge of health, demographic change and wellbeing, the NFU/ ZonMw recommends the following research priorities. These priorities build upon a network approach exploiting systems biology in a systematic and comprehensive manner. Because the
The metabolic syndrome is a network disease in which the interplay between molecules, cells, tissues, organs and the interaction with the outside world is essential, a network approach exploiting systems biology in a systematic and comprehensive manner is the way to tackle such complex diseases.

As lifestyle illnesses are strongly related and dependent on several factors, research must take a multidisciplinary and integrated approach by means of concerted actions. The priorities are mainly oriented on research into, diagnosis of, and therapy/management of network diseases, which require approaches that differ from those that are highly successful for monofactorial diseases. Approaches should target the altered network rather than altered molecules or genes. The public health side of metabolic syndrome and obesity are addressed in NFU-topic 5, collective action for health improvement. The priorities address all aspects of the research and innovation cycle: discovery (insights from science), design (best practices, new products or technology) and deploy (implementation in society). However, given the current status of systems biology, the priorities all start from a discovery oriented, exploratory point of view, and maintain a relative general approach without further subtopics.

1. Insight in pathophysiology

A large bottom up' systems biology oriented programme to unravel the pathophysiology of obesity and its metabolic, endocrinological and cardiovascular consequences as well as its biological origin. The subtopics are:

- The role of nutrition in the pathophysiology of obesity and the metabolic syndrome.
- Fundamental research into the pathophysiology of obesity and the metabolic syndrome.

2. Biomarkers for diagnosis

Identification of biomarkers to discover those individuals at greatest risk for development of comorbidities of obesity and the metabolic syndrome. Building upon the working partnerships of the Dutch Centre for Translational Molecular Medicine (CTMM), a more complete impression of the metabolic make-up of each individual is necessary. Transnational and
trans-sectoral research efforts are needed to support the discovery of indicators of metabolism of fitness of human adipose tissue. The subtopics are:

- Early biomarkers. It is a challenge to identify early biomarkers involved in the development of obesity and the metabolic syndrome. The early origins theory implies that identifying the right biomarkers during the prenatal and early life phase of development is essential in the development of targeted prevention.
- Role of nutrition. The potential role of nutrition for the development of obesity and the metabolic syndrome requires the identification of sound biomarkers of nutritional status. While a lot of research has been conducted in this area, we have not been successful in identifying adequate markers for a number of important nutrients.
- Birth cohorts. Prospective birth cohorts offer the best opportunity to track the impact of biomarkers on adult health outcomes. While animal studies can provide some clues, they can only point the direction for human studies.

3. Large scale European cohort studies
Use of big European cohort studies to generate large scale genomics, proteomics and metabolomics data in combination with intensive phenotyping to enable identification and characterization of gene networks involved in metabolic syndrome. To this end, further development of biobanking infrastructure is pivotal. The subtopics are:

- Comparisons of different populations will play an important role in our understanding of the role of genetics in obesity and the metabolic syndrome.
- Comparison of different populations such as multi-ethnic populations on one or different setting such as different EU countries will enable us to tease out the influence of genes versus the influence of the shared physical, socio-cultural and policy environment.

4. Targeted prevention and treatment
Development of targeted prevention and treatment strategies for subjects at risk. In prevention strategies, food related health research is very relevant. The subtopics are:
Theme 3 - The metabolic syndrome and obesity

- Small-scale intervention studies, set up in an experimental fashion would be needed to provide insights into the individual components driving behaviour and behaviour change.
- Currently, many prevention activities include a range of behaviours and employ a variety of strategies making it difficult to understand what works, why and under which conditions.
- Taking into account the multi-scale nature of obesity, exploration within cross thematic work programme such as ICT for health is needed to define personalized patient approach for prevention, diagnostic and treatment.
- Innovative ICT technologies can be explored to support the integration of biological, pathological and environmental data to model the onset of cardiovascular consequences and evolution of obesity.

Research on the metabolic syndrome and specifically on the priorities presented above is only possible in strong supranational European consortia, lead by scientists from multiple disciplines (such as genetics, biochemistry, biostatistics and social medicine) that work together with clinical researchers and clinicians, patient organisations, and governmental and private public health organizations. In development-oriented projects, SME’s as well as larger business companies could be involved as well, especially in the field of biomarker development. These consortia could build upon and contribute to the existing cohorts, biobanks, standards and other infrastructure.

Rationale for these priorities in EU context

An integrated European approach for metabolic syndrome and obesity includes research on treatment, prevention, genotype-phenotype relationships, sociological background, environmental effects, public health initiatives, and politics. From a European perspective, the challenge of obesity (and the coinciding medical disorder metabolic syndrome) is a typical example of the challenge how to provide better health, while maintaining an economically sustainable healthcare system. In particular for this theme, a better understanding of the relation between environment, behaviour, nutrition, genetics requires new tools and technologies. One of these enabling tools is provided by a number of initiatives developing a
European research approach and research infrastructure on systems biology at large (ERASysBio, Infrastructure for Systems Biology in Europe ISBE). Also, a large number of research groups in Europe are investigating different aspects of metabolic syndrome in a systems biology approach (SBMS). The priorities above align well with these European initiatives, building on the strengths of Europe. In addition, the metabolic syndrome and obesity are major research themes in food research. In fact the Joint programming Initiative on Food is focusing on a Healthy Diet for a Healthy Life in order to comply with the grand challenges in health. ZonMw is chairing the first phase of this JPI, which fits well with the Dutch top sector in food (both research and industry).

Similarly, the Dutch government is committed to counteract the increase of prevalence of obesity and the associated metabolic syndrome and is investing heavily in a systems biology approach (via the Netherlands Consortium of Systems Biology). This supports European research agenda's, and would increase scientific focus and synergy between groups in the UMCs and experts from the agro-food sector. Ongoing research programmes on metabolic syndrome by the UMCs are multidisciplinary and often based on a combination of measurements in biomaterials, imaging data of clinical and population cohorts. Building a joint database and biobank on diabetes (in String of Pearls) is part of these efforts. Also, innovative strategies for prevention and early treatment are developed and tested, both from a public health perspective and as ‘medical prevention’ in the context of healthy ageing. Further collaboration with other member states in this area could be of added value, and requires further ‘end-user’ involvement.
Theme 3 - The metabolic syndrome and obesity

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Theme 4: Regenerative medicine research

Vision

Regenerative medicine (RM) has the opportunity to offer unique health benefits. It is an emerging interdisciplinary field of research for clinical applications for the repair, replacement, or regeneration of cells, tissues, or organs to restore impaired function. It has been hailed as a future revolution in medical care with the aim of helping the body to repair tissue and organs itself. Worldwide socio-economic trends drive innovations for this type of medical treatment: in the year 2000, the lives of over 20 million patients were sustained, supported, or significantly improved by functional organ replacements. The number of people having an organ replaced grew at a rate of over 10% per year. To keep healthcare affordable and to meet the need for higher quality of life, RM could fulfill the demand for better medical treatment by making therapies less invasive and painful, decreasing the need for revision surgery, decreasing side effects, and shortening recovery times. Such therapies can keep people in better physical condition as they grow older and are intended to improve a patient’s well being in general. This will also mitigate the indirect costs of healthcare.

RM uses a combination of biological principles and technological approaches that moves it beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of stem cells, cells of the microenvironment, soluble molecules, material science, genetic/epigenetic engineering, tissue engineering, and advanced cell therapy. The opportunities for regenerative medicines are immense, especially in view of an ever-increasing ageing population with associated ailments: from research into the regeneration of skin, joints, bone, muscle and blood vessels, to the repair of organs like the heart, kidneys and pancreas. However, many hurdles must be overcome before this potentially revolutionary technology can realistically be applied in the clinical practice. In the mean time, technologies and understanding of biology of undifferentiated cells and tissue generation that are being developed in regenerative medicine will have great impact on conventional diagnostic and therapeutic applications. The rate at which RM science
develops is partly dependent on the development of ‘enabling technologies’, such as biomarkers, imaging techniques, high-throughput technologies, and in vitro (e.g. bioreactors) and in vivo modelling systems. These technologies are of great importance for the design, production or in vivo monitoring of new products in the field of RM. Despite the availability of some first generation products, relatively little knowledge is available about the underlying mechanisms of RM. RM holds great promise, but without a significant increase in knowledge about the underlying mechanisms, it will be very difficult to enter into safe and predictable clinical application.

**Topics for the EU research and innovation agenda**

In accordance with an integrated strategy to respond to the societal challenge of health, demographic change and wellbeing, the NFU/ ZonMw recommends the following research priorities. These priorities are based on the fact that RM must face significant challenges to provide a firm knowledge base concerning the wide variety of tissue systems requiring interventions, including molecular, stem cell, microenvironment and tissue-related challenges.

Especially with regard to stem cells considerable basic research is required. Specifically, this will involve (1) isolation, characterization and manipulation of stem cells, (2) understanding the cellular responses in the tissue environment, and (3) studying the interaction between biomaterials and the tissue environment. To meet all these challenges, and to understand how to build complex tissues and organs, we expect that the following lines of basic research be of major importance for the further development of RM and the translation to clinical application:

1. **Understanding cell properties**

New insights into tissue generation, homeostasis and renewal can be obtained through developmental studies. The reprogramming of terminally differentiated cells into pluripotent cells has opened new avenues in regenerative medicine. RM will benefit from the identification of the cell intermediates and molecular mechanisms that may be most amenable to promoting e.g. ex vivo expansion.

Subtopics are:

- Characterizing new/known adult stem cells. Information on the source of normal stem cells, the molecular programs leading to stem cell fate determination and the fixing of the stem cell genetic program through
epigenetic mechanisms is necessary to facilitate stem cell induction, proliferation, and manipulation for use in regenerative medicine. Bona fide stem cell isolation, transcriptome, proteome and epigenome analyses, together with bioinformatics and testing in animal models, will indicate the pivotal epi/genetic factors for stem cell generation and function, providing new molecular intervention strategies.

- Understanding cell lineages and cell differentiation hierarchies. In vitro modelling of stem cell differentiation will allow for identification of the continuous transcriptome, proteome and epigenome changes that are responsible and/or accompany the production of cells functioning in normal tissues. For example, the development of small molecule modulators that promote expansion, manipulation, engraftment and survival of therapeutic cells in RM approaches.

- Reprogramming cells. Direct lineage reprogramming of fibroblasts to other terminally differentiated cells (e.g. cardiomyocytes) without passing through an intervening pluripotent state is another major breakthrough. Much more information is needed before the full potential of these discoveries in regenerative medicine can be explored, such as (1) what is the effect of ‘tissue memory’ on the behaviour of cells, (2) how can we improve reprogramming efficiency, and (3) how functional and stable are the reprogrammed cells.

2. Understanding the interaction of cells with their niche

Both self-renewal of the stem cell compartment and differentiation of tissue specific cells provide normal organ function. This does not occur in isolation, but in the complex cellular architecture of the organ. Cells respond to their structural surrounding and these exhibit unique proliferative and differentiation properties. The application of nanotechnologies to the field of regenerative medicine offers the potential to direct cell fate, thereby supporting the development of therapies/techniques, which are indeed able to regenerate tissues. Subtopics are:

- Dissecting the tissue microenvironment. To regenerate tissues effectively, knowledge of the quantitative balance between the cells of the different lineages and the proper controlled interactions between the lineages normally present in the tissue will need to be realized. Cells of several different lineages are present, including cells for example, of the endothelial, hematopoietic and nervous system.
Theme 4 - Regenerative medicine research

- Recruitment and homing of stem cell: imaging and enhancing stem cell fate, migration and survival. New tools and interventions need to be developed (1) to enhance stem cell recruitment from the bone marrow, (2) to improve stem cell homing and migration, (3) to monitor in vivo tracking of stem cells, (4) to generate scaffolds that mimic the stem cell niche.

- Decellularization of donor organs (e.g. liver, kidney, lung, heart) and tissues (e.g. cartilage) to obtain an acellular three-dimensional biological scaffold that can be repopulated with cells from the patient. Significant problems that need to be tackled are: (1) decellularization methods, (2) choice and characterization of cells to be used to reseed a scaffold, (3) technological hurdles with respect to recellularization of complex acellular scaffolds and (4) design of bioreactors to support whole-organ engineering.

- Design of micro/nanotechnologies enabling the study of single cells (or few cells only). Efforts should be made to develop technologies that (1) allow organization and manipulation of cells and molecules at biologically relevant length scales, (2) enable control of the cellular environment (e.g. extracellular signals that control cell fate or mimic stem cell niches; material surface topographies), (3) enable multi-parameter profiling of single cells (thus deciphering cell functions and phenotypes with cellular resolution), and (4) enable high-throughput screening of agents (siRNA, miRNA, genes, low molecular weight compound libraries) for their regenerative potential. Significant breakthroughs in basic (stem) cell research can be made by applying micro/nano-scale technologies.

3. Strategies to facilitate tissue regeneration

Implanted biomaterials induce an inflammatory reaction known as the Foreign Body Response (FBR). Limited knowledge is available about the underlying mechanisms involved in these reactions and therefore we cannot predict the FBR of a given biomaterial in a given implant site yet. Similarly, the problem of fibrotic reactions needs to be addressed in order to delay progressive tissue destruction. Vitality of larger tissue constructs is critically dependent on the timely development and function of a circulatory system. The current high – and ever increasing – level of understanding of neovascularization enables effective translation into tissue engineering principles. In principle, it should be possible to design a variety of regenerative therapies that are entirely based on the patient’s own biologically active proteins, growth factors, biomaterial scaffolds,
and cells. The community is challenged to develop therapies based on the concept of fully endogenous tissue repair. Subtopics are:

- Understanding molecular and cellular processes in fibrosis in order to develop strategies that can promote healing over scarring. Topics that need to be addressed are: (1) the cellular origin of myofibroblasts, (2) identification of (myo)fibroblast-specific markers in order to monitor these cells, (3) the reversal of myofibroblasts into less fibrotic cells, (4) identification of pathways enabling to increase collagen degradation or decrease collagen synthesis, (5) understanding and steering the response of the immune system involved in healing and scar formation.

- Harnessing the foreign body reaction (FBR). Insight is needed in: (1) recruitment of, and interplay between, the cells attracted to the implant, as well as the phenotypic properties of the cells (e.g. macrophage subsets), (2) the process of cell fusion of macrophages into multinucleated cells, and the role of these giant cells in the outcome of the FBR, (3) the role of the microenvironment in and around the implant in cell performance, (4) the enzymes and their natural inhibitors involved in degradation of biomaterials, and (5) develop materials that induce a controlled FBR thereby protecting the graft from more harmful body response such as inflammation, immune responses or toxic responses.

- Delivering potential drugs to target tissues where regeneration is needed. Because most drugs are likely to be expensive biological molecules (peptides, proteins, DNA/RNA) with cell-specific activities, focus areas should be: (1) protection of the molecules against environmental degradation, (2) cell- or tissue-specific delivery in a dose- and time-correct manner, (3) improvement of transfection efficiency, and (4) formulations that enhance the stability of biomolecules so as to facilitate long-term release.

- Improving the vascularization of tissue engineered constructs. Vascular designs depend on the size and metabolic demand of the tissue. Large and metabolically active tissues such as the heart require a vascular network that can be connected to existing blood vessels of the recipient. In tissues where immediate survival upon transplant is not compromised, one can rely on spontaneous incorporation in the circulation of the recipient. The challenges are therefore: (1) optimizing the vascular design to the grafted tissue and this includes adaption of the vascular cell phenotypes to the particular tissue, (2) creating a vascular network that is stable and functional and (3) non-
destructively studying the fate of graft vasculature and its function after implantation.

- Towards an endogenous in situ regenerative medicine approach. By using the patient's own biologically active components, one may circumvent the excessive cost of commercialization, and the anticipated difficulties of clinical translation and regulatory approval of ex vivo cell expansion and use of artificial biomaterials. An example of a fully endogenous (patient-derived) in situ regenerative therapy is the use of a fibrin scaffold in combination with growth factors from platelet rich plasma and adipose tissue-derived mesenchymal stem cells (expansion of these stem cells are not necessary because of the large quantities found in adipose tissue).

- Addressing tissue complexity. So far this has hardly been addressed in regenerative medicine, though this will be a promising next generation approach, where organs and tissues are being constructed that consist of different cell types (e.g. including endothelial cells additional to bone cells), and that have a certain predefined spatial organization. Novel approaches to address in this topic are the application of 3D biofabrication techniques, in combination with new printable and degradable materials (e.g. hydrogels) with optimized characteristics with respect to mechanical stability, biodegradation behaviour and drug release profiles.

Rationale for these priorities in EU context

A better understanding of the above topics will highly facilitate translating RM into the clinic. Proactive efforts to boost RM today open windows of opportunities for companies and nations to create a new industry driven by unmet medical needs. RM technology, however, is still predominantly in an embryonic, or early growth, stage. Some technologies have reached modest clinical application, but a big breakthrough – such as treatment for a common and currently untreatable disease – is still missing. Resolving a number of challenges will enable RM technology to develop quickly into clinical applications. In the coming years, research should aim to solve fundamental issues, thus enabling value creation and pushing RM towards clinical applications: today's fundamental understanding will enable tomorrow's application. On the discovery side, The Netherlands Initiative for Regenerative Medicine (NIRM) was formed to build the scientific knowledge base and provide synergy in the advances from cutting-edge research in stem cell biology with advances in tissue engineering, so as to improve
existing and create novel regenerative medical treatments. On the design side, the Dutch public private partnership in biomedical materials (BMM) will provide useful insights in the results of combining basic research with clinical application and commercialisation. And current strengths in key technologies such as bioreactors, extracellular matrix reconstruction, scaffolds and drug delivery systems should be further (commercially) exploited. Support may come from imaging technologies that can provide insight in the tracking of cells, for which Europe is creating a research infrastructure. Regenerative medicine is an important sector for Europe; however, it faces growing competition from Asia, notably China and India, and North American regions where there are growing investments in what is perceived to be an industry of the future. Global advances in regenerative medicine have medium and long-term implications that have yet to be addressed in Europe. The pace of change in this complex area affects stakeholders such as national and European regulators, scientific, corporate and clinical sectors, and patients in different Member States. The EC and the Member States should cooperate in addressing topics such as the lack of an internationally unified regulatory framework for stem cell and tissue transplants; the limited commercial investment in embryonic stem cell technology in the EU; the ethical and moral issues challenging various dimensions of Intellectual Property (IP) law, etc. EU governance of this field is highly fragmented because of differences across Member States and the multiple agencies involved. As interaction between states, international bodies and networks become more complex, new forms of multi-level governance, (transnational, public/private, global) become urgent. The setting up of a multidisciplinary European network addressing the above social and policy issues against the background of the scientific challenges is crucial for progress; the NFU supports initiatives to this end. To advance progress in this important field, ZonMw and NWO take part in a group of national funding agencies from 14 European countries that joined forces to launch a cross-disciplinary Research Networking Programme, REMEDIC, supported by the European Science Foundation to identify where the frontiers and future needs are in this complex multidisciplinary high-technology field, by networking researchers and clinicians across Europe. This initiative could form the first step towards more joint programming like activities in regenerative medicine with European Member States, while at the same time safeguarding research programming in competition to maintain the required scientific excellence.
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Theme 5: Collective action for Health improvement

Vision

Ensuring better health is a lifelong endeavour, dependent on prevention, diagnosis, cure, care and effective health and social care systems. Over the past 200 years, Public Health has made enormous contributions to population health. Public Health includes a wide range of interventions and policies both within and outside the healthcare system, mostly aiming at prevention of health problems, such as vaccination and screening programs; lifestyle interventions and health promotion campaigns; work site, spatial planning and environmental measures; and other health protection measures. The challenges to better health are numerous and health inequalities persist across the EU. Infectious disease, maternal, perinatal and nutritional conditions continue to present a significant disease burden and the prospect of emerging health threats remain a concern.

The rising and unsustainable health and social care costs in Europe, (partly) due to its ageing population, is a threat as well: Healthcare spending in OECD countries is rising faster than the rate of economic growth in most European countries and will reach 16% of GDP by 2020. Healthy Ageing has rightly been identified as an important theme, because society will be faced with a double ageing effect: increase of life expectancy and increase of the ageing population as such, due to a baby-boom effect. By 2060, there will be 150 million Europeans over 65, two fifths of whom will be over 80. Population ageing has enormous bearing on participation of citizens in society, which increases the need for cost-effective interventions to delay the onset of disease and disability. Public Health research is necessary to identify entry-points for these interventions. Delaying the onset of disease and disability is also an essential prerequisite for prolonging working life and delaying retirement age. Public Health research is therefore also indispensable to develop interventions and policies aimed at keeping the workforce vital and healthy. Sustainable health improvement for European citizens requires research close to citizens, i.e. population and patient
based studies. With the ageing of the European population, the focus of these studies should increasingly be on common, age-related diseases. Health care institutions will face a change in needs and demands, not only as a result of the societal changes in population, but even more as a result of the increasing prevalence of chronic diseases. Hence, health care institutions will have to adapt their offer to these changing needs. Such changes should be evidence based. Research in this field is known as Health Services research, which is closely related to Public Health research.

Topics for the EU research and innovation agenda
In accordance with an integrated strategy to respond to the societal challenge of health, healthy ageing and wellbeing, the NFU/ZonMw recommends the following research priorities. These priorities also include the prevention and public health related issues from the other NFU themes on healthy ageing, neurodegenerative diseases and metabolic syndrome & obesity. An ageing population is at greater risk of a variety of diseases (including diabetes, mental health disorders and neurodegenerative diseases, musculoskeletal diseases, sensory impairment, allergic disease, various infections and of course, cancer and cardiac disease) and of general frailty and social exclusion. The three research priorities are in the first place societal, ‘deployment’ driven, and would ideally result in best practices that public authorities and their institutions can implement in collaboration with the UMCs. Large-scale studies are necessary and here European partnerships provide added value.

1. Determinants of population health
Development of new prevention programs requires accurate knowledge on the causes and natural history of disease, and therefore relies on the results of epidemiological studies. Variations in exposure and health outcomes within Europe offer great opportunities for increasing the evidence-base for prevention. This also applies to social determinants, which are among the most important factors influencing population health. Two important social determinants are socioeconomic position and ethnicity. All European countries are faced with large and systematic health inequalities between people with a higher and a lower socioeconomic position, and this stubborn health gap is increasingly recognized as an
important barrier for overall progress in population health. All European countries have also been faced with considerable migration flows, which have increased the number of foreign-born immigrants, and introduced new sources of variation in population health. What are the main determinants of these inequalities in health, and what do they imply for health policy?

Answers on questions like these are increasingly vital for designing effective prevention policies in Europe. Over the past decade, new opportunities for such analyses have arisen based on the establishment of new cohort studies and new data-linkages between routinely collected data. In view of the enormous variations in health within Europe this is likely to lead to many new insights into the explanation of health inequalities, e.g. on the role of lifestyle factors, of the physical and social environment, and of lack of access to inadequate health care.

2. Effectiveness of prevention programs

Building up a scientific evidence base for prevention is a huge challenge, because the evaluation of large-scale interventions (e.g. vaccination, screening, population-wide tobacco or alcohol control) requires large-scale studies, which are often beyond the scope of national funding agencies. Pooling evaluation resources within a European framework, and conducting large-scale evaluation studies on the basis of common priorities will therefore help in speeding up the growth of the evidence-base. In more detail, two subtopics are:

- Some of these interventions can only be studied as ‘natural experiments’, namely when it is impossible to experimentally assign individuals or groups to the intervention and a control condition. This applies especially to policies tackling ‘upstream’ determinants, such as the physical environment, poverty and other aspects of socio-economic disadvantage, etc. Taking advantage of ‘natural experiments’, in which one compares health outcomes between a country (or region, or city) where the policy was implemented, with those in a country (or region, or city) where this did not occur, may then be the best possible evaluation design. Studying the effects of these interventions within a European context may then make it easier to find appropriate control conditions.
- One risk factor deserves special attention: physical inactivity. Physical inactivity is widespread throughout Europe, and is one of the most important causes of burden of disease in the European region. This has led to the recognition that cost-effective physical activity; sports and exercise interventions are needed at the level of prevention, cure and care. International research projects on these issues are indispensable to increase learning speed.

3. Identification of best practices in health policy
There are large variations between European countries in the effectiveness of their health policies: some countries have been considerably more successful than others in e.g. tackling smoking or excessive alcohol use, or reaching large sections of the population with vaccination or screening programs. Identifying best practices, and analysing the determinants of success, may help all European countries in improving their health outcomes. What are the institutional determinants of success or failure of health policy? Why are collective actions for health improvement higher on the political agenda in some countries than in others? What can other countries learn from countries, which have consistently been more successful in improving population health?

In many European countries there is increasing focus on the role of the curative sector in delivering preventive care. What are the best practices in this area when one compares different European countries? What can we learn about the conditions under which integration of preventive care in the curative sector is successful? Cross-border European Public Health research on these topics is vital, and funding can only be found on a European rather than a national level.

Rationale for these priorities in EU context
The main challenge is to optimize the delivery of healthcare to European citizens in view of an ageing population, new threats and increasing costs. The European Commission 2007 White Paper on Health acknowledges that investments in research are needed to develop effective public health interventions and policies against modern health threats. The NFU underlines the importance of Public Health research, not only at a national but also at a European level. In particular because public health research
on the priorities presented above is only possible in strong supranational European consortia, in which multidisciplinary players from many different sections of the society are represented, such as universities, medical schools, national as well as local and governmental as well as private public health organizations and SME’s as well as larger business companies. In this field, the UMC’s are keen to take on their responsibility. Therefore, prevention and public health research has to be higher on the agenda of national governments and the European Commission, because a substantial fraction of all health problems is avoidable. Prevention will not only improve population health, but may also improve the financial sustainability of health care systems. New and more effective means of prevention will only come available through scientific research, particularly international public health research. The NFU strongly recommends increasing the funding possibilities for collaborative public health research in the future EU research funding programs; in FP7 funding of public health research remained too limited.

A European approach and international cooperation should lead to better understanding and management of the relation between environment, behaviour, nutrition and genetics. Over the years several initiatives have been initiated to combine existing population based studies. The EC should support these initiatives, take the lead in the standardization of measurements and design, and stimulate the inclusion of both personal and group level environmental factors in these studies. This fits well into the Public Health programme of DG Health and Consumers, which aims to bring more synergy between research, innovation and regional funding in order to accelerate the transfer of knowledge into products and services that are beneficial for EU patients and citizens at large. The Netherlands has a leading position in Public Health research in Europe and is well equipped to initiate and organize consortia. It has strong research traditions in epidemiology, health promotion, health economies, and other contributing disciplines. In order to create synergy, the NFU is aware of the fact that the UMCs can share their expertise with Europe and other Member states. Further collaboration is of added value, and requires further ‘end-user’ involvement. As the public health domain is mainly public, sharing expertise would include working with a range of national public health institutes as well.
Theme 5 - Collective action for Health improvement

Netherlands Federation of university medical centers
in cooperation with ZonMw

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Theme 6: Biobanking

Vision

Biobanking is essential for science-based health care solutions in the 21st century. In order to develop better diagnosis, treatment and cure for diseases a deeper understanding is needed of genetic and environmental pathways causing disease, including mechanisms that protect people from becoming ill. This knowledge needs to be translated into preventive, diagnostic and curative applications. Scientific research aimed at these issues depends on the availability of a broad spectrum of high quality human biological samples related to health and disease, accompanied by clinical, environmental and lifestyle data. Biobanks provide these essential resources.

Member States have identified that the major burden of disease for all European health systems comes from diseases caused by a combination of genetic, environmental and lifestyle factors (multifactorial diseases). To understand the contribution of genetic variation and the impact of influences from the environment, the numbers of samples from patients and healthy control persons that are needed to achieve statistical significance exceed the scale of individual biobanks and cohort studies. Only by combining material and linking data enough statistical power can be achieved to answer questions about multifactorial diseases like cancer, diabetes, rheumatism, cardiovascular disease, depression, asthma or Alzheimer's. Real breakthroughs can thus be expected from scaling up, interconnecting and creating networks of existing biobanks, thereby creating added value, and avoiding duplication of efforts.
Topics for the EU research and innovation agenda

In accordance with an integrated strategy to respond to the societal challenge of health, healthy ageing and personalised medicine, the NFU/ZonMw recommends the following research priorities. These priorities build upon the BBMRI-EU plan for a European Infrastructure Consortium (ERIC) legal entity, and the Dutch BBMRI-NL contribution to this EU initiative. They address scientific, infrastructural and competitiveness aspects, thereby complying with a number European policies (see below) from which European citizens should benefit:

1. Biobanking for scientific research

A globally unmatched, Europe-wide platform for translational medical research is envisaged with the aim to develop personalised medicine and disease prevention for the benefit of European citizens. Collections include the attached data on factors such as health status, nutrition, lifestyle, and environmental exposure of the study subjects. Combined with the expertise of the clinicians, pathologists, bio-informaticians, and molecular biologists involved, translation of scientific discoveries should result into benefits for society by identifying prognostic and diagnostic biomarkers and pharmaceutical targets. International collaboration requires further developing of international standards. And sustainable, standardised sample and datasets are a prerequisite for long term follow up research.

To support scientific research priorities are:
- Biobank enrichment and harmonization, to enable large-scale (international) scientific cooperation
- Specific applications such as targets for drug discovery, biomarkers for drug development, new diagnostics, personalized medicine and public health applications.
- Strengthening and upgrading the IT infrastructure for interoperability and large scale datamanagement and analysis
2. **Biobanking as research infrastructure**

A European infrastructure improves the accessibility and interoperability of the existing comprehensive collections, either population-based or clinical-oriented, of biological samples from different (sub)populations of Europe. The infrastructure needs to provide:

- Free access to documents, Standard Operating Procedures (SOP’s) and best practices developed by BBMRI-ERIC,
- Open access to published results and data published in coordination with partners of BBMRI-ERIC, in accordance with the Berlin declaration (2003).
- Fair access to samples and related clinical data. Fair access is primarily based on international scientific peer review and ethical review of the research project proposal.
- Participating Members States agree on BBMRI-ERIC Statutes, and individual banks on the Partner Charter with its National Node.
- Services Contracts and Material Transfer Agreements
- Harmonization of Ethical, Legal and Societal Issues (ELSI) to achieve standards and guidelines that properly balance individual values, such as protection of privacy and informed consent, with shared values of facilitated access to progress in health care and disease prevention.

The BBMRI-ERIC is aiming to be the European part of the Global Biological Resource Centres Network (GBRCN).

3. **Biobanking for competitiveness**

To fully realise the enormous potential of European biobanking, also biotech and pharmaceutical industry must have a possibility to collaborate with academic researchers. Access to BBMRI-ERIC also foresees special solutions for industry by establishing:

- Expert Centres that can be established as public-private-partnerships, and perform the primary analysis of biological samples in a pre-competitive setting using latest technologies under standardized conditions, with professional quality management and operating on a non-for-profit basis. Data generation in Expert Centres will also lead to more efficient use of finite resources and improves sharing of the research data generated. Expert Centres will also lead to a repositioning of intellectual property and enhance competitiveness of Europe’s large
industry as well as SME's by fostering collaboration thereby contributing to the goals of the Innovation Union Initiative.

- Associated Technology Transfer Centres

By doing this, the International competitive position of pharmaceutical and life science industries in Europe will improve; Major companies have already expressed their interest in BBMRI Expert Centres.

**Rationale for these priorities in EU context**

To meet the grand challenges in health, the creation and maintenance of world-class research infrastructures in Europe is imperative. The European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) is one of them. In its preparatory phase (2008-2011), BBMRI planned for a distributed research infrastructure with operational units in all participating countries. The next step is to become a European Research Infrastructure Consortium (ERIC). BBMRI-ERIC complies with the European policy for sustainable health care for ageing populations and personalized medicine and with measures to improve health inequality in eastern European countries. It also contributes to the Cohesion Policy and implementing the Innovation Union, supporting Europe's response to pandemics and security threats. In doing so, BBMRI-ERIC intend to be a fundamental component in addressing the ongoing and future requirements particularly of the EU's health services framework including competitiveness and innovativeness of health-related industries.

The Netherlands is having a key position in BBMRI-EU: The Dutch government has committed itself to becoming a partner in the European legal entity by signing a Memorandum of Understanding (MoU) for the BBMRI-ERIC application. BBMRI-NL is the Dutch national hub, linking over 150 Dutch biobanks, including clinical and population cohorts, to BBMRI’s hub and spoke infrastructure. Several Dutch biobanks participate in European consortia, and in order to create synergy, the NFU is aware of the fact that the UMCs can share their expertise with Europe and other Member states. Since 2007, the Dutch government has funded three major biobanking projects, which are all dedicated to building a biobank infrastructure: String of Pearls (PSI), Lifelines and BBMRI-NL, with essentially different objectives. The NFU supports all three to stimulate coherence and synergy in this area. A proposal for funding of the next
Theme 6 - Biobanking

period includes the creation of a national, or Dutch Biobank Hub (DBH), which will explicitly formalise the tripartite collaboration, and will secure continuation of BBMRI-NL.
Theme 6 - Biobanking

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Theme 7: Clinical research

Vision

Clinical research refers to the evaluation of diagnostic, prognostic and therapeutic medical interventions (e.g. pharmaceutical, medical device) in human populations on efficacy, effectiveness, and efficiency, following rigorous methodology. It encompasses research designs that range from prospective observational cohort studies and registries to rigorous clinical trials. The latter span first human testing, proof of concept trials and large, and increasingly global, trials to evaluate therapy in the target population. Clinical trials are thus at the core of Evidence Based Medicine. Currently, large unexplained variations in healthcare practices exist, and many healthcare interventions are not yet based on solid evidence from clinical research. In view of the rising costs of healthcare, the lack of evidence on the efficacy, effectiveness, and efficiency of healthcare, interventions is increasingly socially unacceptable. Particularly evidence of relative effectiveness of treatment alternatives for the same condition is often lacking. Such evidence is, for instance, not part of a usual development program to obtain a market authorisation for a new pharmaceutical. It is evident, however, that more solid evidence of this relative effectiveness and safety can significantly contribute to patient safety and healthcare efficiency.

Clinical research is thus an essential component of quality health research systems. The primary goal of clinical research is to create and apply clinically relevant knowledge. A strong research infrastructure within research institutes and academic medical centers contributes to a vital and sustainable clinical research culture, which is a cornerstone in health research and for preserving human health. Improving the research infrastructure for investigator driven clinical research is crucial to address societal and scientific challenges, including the quicker and safer introduction of innovations for patients. It is paramount that the public funded health research sector has sufficiently countervailing power, in order to steer, design and conduct clinical research into societal
relevant questions. Moreover, sufficient public and public/private funding is crucial to enable the execution of the necessary clinical research by consortia of academic medical centers and institutions.

Topics for the EU research agenda
In accordance with an integrated strategy to respond to the societal challenge of health, healthy ageing and personalised medicine, the NFU/ZonMw recommends the following research priorities. University Medical Centers have a special responsibility towards the performance of clinical research, as they combine the necessary scientific expertise with access to patients. In present day clinical research, international and preferable global collaboration is often needed to ensure the number and diversity of participants needed for the validity and usability of the trial results. Another trend in health care in Europe is that treatment and care of important diseases, such as diabetes, mental illnesses, and some forms of cancer, are increasingly brought to the primary care setting. In this setting and with an aging population, this is highly complex in view of the multiple co-morbidities and associated treatments, as well as the lack of infrastructure to perform research related assessments. The Netherlands is among the European countries most advanced in clinical research in the primary care setting. The NFU would therefore like to recommend the following, primarily investigator driven, topics on clinical research:

1. Clinical trials in primary care setting
Demand for high quality research in primary care is growing, particularly multicentre (cluster) randomised controlled trials. Such studies are difficult to conduct, disruptive to routine practice, and may fail to recruit enough general practitioners or patients. Several factors are known to influence general practitioners’ participation in research. Based on the Dutch experience, networks of primary care practices facilitated and trained through academic institutions offer a way to overcome most barriers. Furthermore, scientific methodology as well as smart logistical operations need to be further developed to accommodate clinical research in such a geographically and demographically dispersed setting. The number of practices needed is usually large and each of them small in patient numbers. Clinical research in primary care setting thus needs further
investment to meet the challenges in the health care system in a demographically challenging future.

2. *Methods for individual patient data meta-analytical techniques*
By using individual patient data (IPD) to perform meta-analyses, the accuracy of tests can be assessed in relation to other patient characteristics and allows the development or evaluation of diagnostic algorithms for individual patients. Further development of this type of methodology is needed to overcome the lack of information, together with variations in design and quality of studies, that hamper meta-analyses based studies on the accuracy of tests in real practice.

3. *Evaluation of multiple treatments in cost effectiveness*
In order to evaluate multiple treatments, the usual cost effectiveness analysis in which the costs are compared with the clinical effects (e.g. cost per life years gained), may need to be replaced by cost-utility analysis in which outcomes are measured in terms of social value (cost per quality-adjusted life years or QALY). This needs further investigation.

4. *Comparative effectiveness research*
Decision making in health care reimbursement strongly depends on knowledge on the comparative effectiveness and efficiency of clinical interventions. This is highly relevant for the major diseases, where for many drug therapies head-to-head comparisons of new pharmaceutical therapies on comparative effectiveness are lacking or insufficient at the time of market authorization. And it is especially important for clinical research into rare diseases, or several types of non-medicinal products (devices, techniques, diagnostics, prognostics), and studies in smaller populations which are commercially less interesting for industry, but very relevant for patients and consumers. Comparative effectiveness research (CER) identifies what works best for which patients under what circumstances.
5. Personalized medicine & companion diagnostics

Therapeutic treatment with monoclonal antibodies has been approved by the EMA for more than 25 different antibodies. However, inter-individual immune system differences and complex interactions, requires careful monitoring of the intervention by specific ‘companion diagnostics’. Development of these companion diagnostics is only possible through close collaboration between academia and industry.

Rationale for these priorities in EU context

Through the ESFRI Roadmap a European research infrastructure for multinational clinical research started: ECRIN, the European Clinical Research Infrastructures Network aims at further developing and connecting a EU wide distributed research infrastructure. Through its national coordinators, existing academic research infrastructure in different countries is connected and made available at a larger scale. ECRIN can also offer, in collaboration with national partners, integrated support to multinational clinical research projects through information, consultancy, and a set of flexible services. In its program it has specific attention for orphan diseases, medical devices and nutrition. This support is provided by the distributed infrastructure connecting national ECRIN partners (networks of Clinical Research Centers or Clinical Trials Units). Similarly, the European Advanced Translational Research Infrastructure in Medicine (EATRIS) aims to be a European, globally competitive infrastructure for biomedical translational research to optimise the outputs of both basic and clinical research. EATRIS overlaps slightly with ECRIN: Latest exit point for EATRIS projects is the proof-of-concept in human (e.g. up to clinical phase I/IIa).

The Royal Academy of Sciences in the Netherlands has called upon the government to strengthen the public clinical research infrastructure in the Netherlands. The NFU has recently implemented policy to further improve the standard of quality of clinical research, addressing aspects ranging from responsibilities and study management, data monitoring committees to monitoring and auditing. This NFU quality platform will represent the Netherlands in ECRIN. Alignment with EATRIS is secured because the chairing seat of EATRIS is based in the Netherlands as well. Academia, professionals, regulators, and industry collaborate in public-private
platforms such as FIGON and the Dutch Clinical Trial Foundation (DCTF), to strengthen the interactions between all partners, to further improve expertise and education of professionals, to stimulate the international position of the Netherlands in a European context, to increase access of patients to clinical trials, and to generally contribute to a quality clinical trial infrastructure. Further collaboration with other member states in this area could be of added value.
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Theme 8: Bioimaging

Vision

Imaging techniques are essential tools for both scientists and medical doctors to understand living systems in health and disease, at the molecular, cellular and physiological level, from biological model systems to patients. Imaging is unique in that it allows the non-invasive assessment of structural and functional changes of cells and organs that may reflect specific pathology. A recent wave of technological developments holds great promise for fundamental, clinical and epidemiologic research. Developments in advanced microscopy focus at visualizing dynamic processed within a single living cell, whereas medical (population) imaging focuses at cells and tissues in patients. Together these techniques cover bioimaging from molecule to man. Moreover, the tools originally developed for research are continuously gaining ground in therapeutic applications. Within the framework of EuroBioImaging, in particular super resolution microscopy, ultra-high field MR imaging, phase-contrast CT, MEG-MRI, correlative light/electron microscopy and high throughput - high definition microscopy for systems biology are highlighted for further development, thus representing both Advance microscopy and medical imaging.

The future of medicine lies in early diagnosis and individually tailored treatments, a concept, which has been designated ‘Personalized Medicine’ (PM): delivering the right treatment to the right patient at the right time. However, the value of medical imaging in PM is frequently underestimated, as many policy makers forget the all-important ‘right location’ in the PM paradigm. (Medical) Imaging has always been personalized as it provides individual assessment of the location and extent of an abnormality, and in the future it will prove fundamental to almost all aspects of PM. Stratification based on imaging biomarkers can help identify individuals for preventive intervention and can improve disease staging. In vivo visualization of locoregional physiological, biochemical, and biological processes using molecular imaging can detect diseases in pre-symptomatic phases or facilitate
individualized drug delivery. Furthermore, imaging is essential to patient-tailored therapy planning, therapy monitoring, and follow-up of disease progression, as well as targeting non-/minimally-invasive treatments, especially with the rise of theranostics.

**Topics for the EU research and innovation agenda**

In accordance with an integrated strategy to respond to the societal challenge of health, healthy ageing and personalised medicine, the NFU/ZonMw recommends the following research priorities for bioimaging. These priorities are aligned with and build upon the strategic agenda for the EuroBioimaging Preparatory Phase. EuroBioImaging is developing a plan to construct and operate a set of complementary and strongly interlinked infrastructure facilities appropriately distributed across the European member states. The topics address all aspects of the research and innovation cycle: discovery (insights from science), design (best practices, new products or technology) and deploy (implementation in society).

1. **Discovery**
   - Cellular life sciences research in diagnostics, pathophysiology and development of personalized medicine using systems biology approaches, especially in connection with light microscopy approaches.
   - Application of functional (morphologic) imaging to genetic association studies; population imaging.

2. **Design**
   - Image processing & quantitative image processing, validation of imaging biomarkers
   - Functional drug studies in which imaging is used to provide biomarkers or surrogate endpoints for new drugs. Here we complement French and German strengths

3. **Deploy**
   - Functional and structural imaging in psychiatry;

**Rationale for these priorities in EU context**
Through the ESFRI Roadmap a European research infrastructure for imaging technologies was created: EuroBioImaging. This research infrastructure aims to become an engine that will drive European innovation in imaging research and technologies by sharing of best practice and image data. Via a combination of technological and strategic objectives, EuroBioImaging will provide the key elements for a successful biomedical imaging infrastructure across Europe, covering the full scale of biological and medical applications. By forming nodes in the ESFRI Member States it will create a widely distributed and strongly coordinated infrastructure to support research, training and innovation and provide broad access to “beyond state of the art” imaging technologies that are otherwise not accessible to the biomedical community. Hence, EuroBioImaging will address the fragmentation of imaging efforts currently present in Europe. An imaging research infrastructure for basic and applied research opens the possibility for population imaging: to investigate specific pathophysiological substrates of diseases in a pre-symptomatic phase, in an epidemiological context, and at the population level. The ultimate aim of population imaging is to help develop the implementation of strategies to prevent disease. On a more general level, it creates the possibility to apply the full range of imaging techniques to address current major health issues in our society.

The Dutch strength in imaging research is due to substantial European funding as well as from charity funds, the Heart Foundation in particular. The NFU has supported and helped initiating the population Imaging Infrastructure PI2, which collaborates with and is integrated in the EuroBioimaging infrastructure. Also, other initiatives are developing, having a mainly scientific research orientation that is carried out in partnership with industry like Philips and Siemens, but also smaller companies. Connection with other public research & innovation funding organisations (‘public’) or charity organisations (‘people’) is catching up and provide best practices of how the value chain can benefit from an integrated approach. Further collaboration with other member states in this area could be of added value, both for technological complementarities as for the application of imaging in a range of disease oriented research.
Theme 8 - Bioimaging

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