NATIONAL PLAN – RESEARCH AGENDA FOR Sustainable Health

NATIONAL PLAN ACADEMIC MEDICINE, BIOMEDICAL SCIENCE AND HEALTHCARE RESEARCH
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Preface

Health and healthcare are trending topics. Many of the questions submitted to the Dutch National Research Agenda were about health. The Netherlands is also concerned about its healthcare system. A great deal can be done already, but better and often expensive treatments are added continuously. Science stands for nothing, but how can we keep everything that is or will become possible affordable? Will we soon spend a quarter of our household incomes on care?

Everyone is convinced that care provision cannot grow indefinitely. The sustainability of our system is under pressure. Therefore, prevention, preventing disease by improving health literacy, healthier lifestyle, early detection of disease risks and new personalised treatments will be high on the research agendas in the coming years, and this can contribute substantially to healthy ageing, which is of social and economic importance. The role of science as a driving force behind sustainable and innovative care is therefore more important than ever.

The transition to sustainable healthcare requires all stakeholders in healthcare to join forces. This National Plan describes the approach of the Dutch University Medical Centres (UMCs), of course in close collaboration with universities and other knowledge institutions. This plan constitutes an elaboration of the Dutch National Research Agenda in the areas of academic medicine, biomedical science and health research. The National Plan will be developed further based on the National Research Agenda "route workshops", particularly in the areas of health research-prevention-treatment, personalized medicine and regenerative medicine.

Scientific collaboration and innovation are the key to utilising the available resources as efficiently and effectively as possible. This is the only way to realise sustainable care. In addition, this is the only way for Europe to keep performing above average and to keep excelling at the international scientific top.

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Summary

Sustainable health is the common goal of the eight Dutch University Medical Centres (UMCs). Sustainable health entails keeping people healthy at reasonable cost. It is also about keeping our healthcare accessible, affordable and high quality. And it entails training the best medical doctors and other healthcare professionals. Collaboration of strategic partners such as healthcare organisations, insurance companies, public authorities, industry, healthcare professionals and citizens is essential to achieve a sustainable healthcare system. The complete chain from basic research to a more personalised approach of prevention and treatment, as well as the financial implications, will determine if we can bring the sustainable health goal closer. Sustainability is essential because healthcare costs will become irresponsibly high if policies are not changed. In addition, the number of hospital patients will become too large to be handled by healthcare professionals and we will not be able to deliver appropriate care to the growing group of vulnerable elderly people. Recent scientific developments offer great opportunities to force breakthroughs in the coming years. The Netherlands can make a major contribution to this.

The UMCs are in an excellent position to reach the sustainable health goals, together with their partners in patient care, education and scientific research. First and foremost this is because of the unique Dutch construct of a University Medical Centre, with short lines of communication between fundamental biomedical research and clinical applications, and a strong focus on the translation between the two. The UMCs’ strong competitive position in international scientific research in the Life Sciences & Health sector (LSH) is based on this hallmark. The UMCs can contribute to the broad implementation of scientific knowledge by virtue of their networks in healthcare and prevention. Valorisation is another implementation form of biomedical knowledge. The UMCs are increasingly considering this translation to the market, with important societal and economic consequences. The UMCs also excel in evaluating new developments in efficiency and cost-effectiveness.

CORE THEMES OF THE RESEARCH AGENDA
Sustainable health will be facilitated by societal, scientific and technological developments. Relevant social developments include an increased health literacy and empowerment of patients, as well as new connections between prevention, work, sports, healthcare and housing. Biomedical research is producing increasingly detailed knowledge about the aetiology and course of diseases. This creates opportunities for preventing disease and preventing chronicity through early intervention in disease processes. Relevant technological developments include everyday ICT solutions (e.g., the smartphone is the basis for many e-health applications), high-quality data structures (required because of the big data revolution), but also the increasing interaction between technology and biology in measurement tools, imaging techniques and organs-on-a-chip.

Personalised medicine (patient-centred) and personalised health (focusing on healthy citizens) will revolutionise both healthcare and prevention in the coming years. Detailed knowledge about
the significance of measurements (biomarkers) facilitates tailored treatments, with more effect and less side-effects. Knowledge derived from biobanks and big data is the most important foundation for personalised medicine and personalised health.

The broad development and implementation of personalised medicine and health requires collaboration between technological knowledge institutes, universities, UMCs, industry, patient organisations, insurance companies and societal partners. If these developments fulfil their promises, the Dutch healthcare and prevention system will become significantly more efficient and effective.

Regenerative medicine – repairing tissues and organs using stem cells, biomaterials or biochemicals – may help elderly people to live independently for longer, requiring less care. This field also requires additional research to translate the first success stories into widely applicable techniques. This concerns basic research in the field of stem cells, tissue environment (extracellular matrix) and biomaterials. In addition, it concerns applied research with the aim to produce and evaluate artificial tissues and organs.

At present, large-scale facilities for storing human samples (biobanks) and for storing and exchanging data are crucial determinants of the progress of the life sciences. The Netherlands Federation of UMCs (NFU) has already started and supported many initiatives in these areas, including the collaborative biobanking infrastructure BBMRI-NL2.0 and the NFU programme Data4lifesciences, in collaboration with the Dutch Techcentre for Life Sciences (DTL), SURF (ICT partnership of Dutch education and research institutes), the Netherlands eScience Center, the Center for Information Technology (CIT), and others. However, the continuity and long-term funding of these initiatives is a point of concern. In general, the various infrastructures have become essential to the life sciences. This has prompted the NFU to explicitly call attention to sustainable infrastructures in the Netherlands and in Europe.

Collaboration and coordination are becoming increasingly important in this context.

Education requires specific attention, i.e., education of students, training of medical specialists and general practitioners, continuing education of these professionals and education programmes for researchers and other healthcare professionals. The UMCs are directly involved in all these forms of education. They regard education as an important opportunity to further improve healthcare quality and to implement the scientific developments towards sustainable healthcare in practice.

The steps towards sustainable healthcare described here are already in full progress within the UMCs and their partners in the Netherlands and abroad. This National Plan shows the steps required in the near future to ensure that the Dutch healthcare system and economy can benefit from these promising developments.
The Dutch healthcare system is facing significant challenges. The population of the Netherlands is ageing, while the workforce decreases. The country is expected to be home to 4.8 million people over 65 by 2040. Since most chronic diseases manifest themselves in the second half of life, this results in an increasing pressure on a healthcare system that has to cope with less manpower.

Great progress has been made in unravelling the aetiology of diseases, making novel and successful treatments available. However, these treatments may be expensive, thus contributing to the rising cost of care. The nature of diseases is also changing as a result of improved paediatric treatment options (in the case of rare diseases, e.g., juvenile rheumatoid arthritis, cystic fibrosis and oncological diseases). Moreover, all age classes are increasingly affected by diseases of affluence, e.g., metabolic syndrome, diabetes, arthritis and cardiovascular disease. In addition, the number of people with mental health problems increases. We are also confronted with unpredictable diseases, such as infections, that could have a major impact on society because they are spreading much more easily than before due to increased travelling and migration of people and due to increased antimicrobial resistance.
Examples of questions submitted to the Dutch National Research Agenda:

**CHRONIC DISORDERS**
What are the consequences of chronic disorders, stress and disability, and what is the best way to cope with them?

**AFFORDABLE**
How can we achieve the best possible health care quality, while keeping it affordable?

**INTESTINAL DISORDERS**
Intestinal disorders, in particular the relationship between gut flora and health: what can we do to benefit our gut flora?

**UNEXPLAINED SYMPTOMS**
Can we gain a better understanding of the factors that play a role in the occurrence and persistence of medically unexplained physical symptoms, leading to better treatments of them?
The sustainability of our healthcare system is under pressure; everyone is convinced that care provision cannot grow indefinitely. Therefore, prevention (i.e., preventing disease by improving health literacy, encouraging healthy lifestyles and early detection of health risks) will be high on the agenda in the coming years. Prevention will also contribute substantially to the broadly supported social and economic importance of healthy ageing.

Dutch research and innovation hold a strong position in the international Life Sciences and Health (LSH) sector. International rankings reflect the strength of Dutch biomedical research. This sector offers great opportunities for further development of an effective and sustainable healthcare system because of its unique combination of knowledge and skills. The Dutch knowledge institutes (i.e., UMCs, universities, universities of technology, applied research institutes, collaborating top-clinical education hospitals and universities of applied sciences), scientific institutes (e.g., Netherlands Cancer Institute, Hubrecht Institute and other institutes of the Royal Netherlands Academy of Arts and Sciences ‘KNAW’ and the Netherlands Organisation for Scientific Research ‘NWO’) and health funds (e.g., Dutch Cancer Society, Dutch Heart Foundation, Lung Foundation Netherlands and Dutch Arthritis Foundation) are strategically well-positioned to make fast and efficient progress. Crossovers with closely related sectors, such as Agro-Food and High-Tech Systems & Materials, offer additional opportunities for promising innovations.

Last year, the so-called ‘Dutch National Research Agenda’ was drawn up by a knowledge coalition consisting of VSNU, KNAW, TNO, TO2, VNO-NCW, MKB-Nederland, NWO, VH and the NFU. This research agenda contains the research questions that academic research will focus on in the coming years. The agenda was based on citizens’ questions to science. The agenda is an elaboration of the ‘2025 Vision for Science, choices for the future’ of November 2014, in which the Dutch government expressed its scientific ambitions. The Dutch National Research Agenda is related to the ‘top sector policy’, the second flow of funds policy and the funding programmes of the Netherlands Organisation for Health Research and Development (ZonMw). Many of the questions submitted to the Dutch National Research Agenda were related to health and healthcare. The UMCs account for more than 90% of the total Dutch academic scientific output within the life sciences (NOWT, 2010). Therefore, they will take responsibility to further elaborate the health topics on the Dutch National Research Agenda.

To this end, the NFU has prepared the present National Plan. The plan should guide the development of academic medicine as well as biomedical and healthcare research within the UMCs in the next five years. It also addresses the development of the life sciences sector as a whole.
The Netherlands has every reason to be proud of its eight UMCs. The combination of high-quality scientific research, patient care and education within one organisation is unique. Many countries, including Belgium, Norway and Ireland, have shown interest in applying this Dutch model in their own country.

The strong interrelationship between science, patient care and education within the UMCs enables them to deliver the best possible care, applying the latest insights in healthcare. The way in which UMCs are organised, which is unique in the world, makes it possible for a single institute to cover the whole spectrum from basic exploration, through translational research and patient-related research, to clinical applications. This is an important source of care renewal. Conversely, observations in patients may generate new hypotheses to be explored with basic or experimental translational research, increasing our knowledge. This is a fruitful approach: the Dutch UMCs rank among the world leaders in science. Internationally, they are in third place (CWTS, 2012). Taken together, the UMCs publish around 40% of the total Dutch scientific output. They are thus major contributors to the Netherlands’ knowledge economy.
Examples of questions submitted to the Dutch National Research Agenda:

**DIAGNOSTICS**
How can we improve diagnostics, treatment and vaccines for immune disorders and infectious diseases?

**FUNDAMENTAL RESEARCH**
How can we improve the translation of fundamental biomedical research into the development of new drugs?

**VITAL AND HEALTHY**
How can we develop new drugs and other treatments that will keep us as healthy and vital for as long as possible?
The UMCs have recently increased their cooperation in NFU context in the areas of patient care, education, scientific research and infrastructural investments. The UMCs have jointly invested in biobanks such as LifeLines and the String of Pearls Initiative, in bioinformatics and data handling, and in translational and clinical research. This reinforces innovative research and, as a result, it strengthens the scientific and economic competitiveness of The Netherlands.

**Economically Relevant**
The impact of the UMCs on the Dutch economy is considerable: each euro invested in the joint UMCs results in four euro added value. With a total number of about 70,000 employees, the UMCs are major employers, often the biggest in their region. The UMC network generates a total impact of 20.4 billion euros added value and it supports more than 215,000 jobs across the Netherlands (BiGGAR report, 2014). This includes employees that work in and in the direct vicinity of the UMCs, the UMCs’ expenses, the money that employees spend in the local economy, the UMCs’ projects, as well as expenses of students and student employment outside the UMCs. Public-private partnerships are important: many UMCs constitute the heart of a campus with a high density of innovative companies. The sector Life Sciences & Health contributes 2.5% to the Dutch gross national product and thus makes a substantial contribution to the Dutch economy. The basic and more applied research within UMCs is an important prerequisite to achieve innovations. Therefore, the UMCs participate in the top sectors Agri & Food and High Tech Systems & Materials in addition to the top sector Life Sciences & Health. The UMCs also actively contribute to the Knowledge and Innovation Agendas 2016-2019 of the top sector policy of the Dutch government.

Public health protection and health promotion are other ways to improve public health. The UMCs can play a role in increasing the effectiveness of public health measures, by producing knowledge about behavioural factors, social determinants, environmental factors, screening programmes, organisational conditions, health economics, and global health and nursing research.

**Networks**
Collaboration among healthcare providers is the key to higher quality, more comfortable and more cost-effective patient care. To this end, the UMCs have formed networks with other healthcare providers. These networks have organised proper care for specific patient groups, e.g., oncological networks. The networks perform applied research to further improve their patient care. They promote knowledge exchange and their research programmes make use of the strong scientific and infrastructural base of the UMCs. The common thread of these networks is shared responsibility for improving the quality and cost-effectiveness of care, and promoting innovation. The patient’s wishes play a central role in this.

These networks also form the backbone of education and training of healthcare professionals. UMCs and education hospitals collaborate in so-called ‘Education and Training Regions’, for example to train medical specialists. In addition, the networks facilitate internationally competitive clinical scientific research, coordinated by the UMC and conducted within the associated hospitals.
This enables researchers to rapidly compile large groups of patients for research purposes. Furthermore, the Dutch Ministry of Health, Welfare and Sport has announced the implementation of local health and prevention networks to fight antimicrobial resistant microorganisms. These local networks will require all healthcare institutions within a region to collaborate. The UMCs connect the institutions and take a leading role in almost all healthcare regions.

**EDUCATION**

The UMCs’ education programmes and the training of general practitioners, medical specialists and other healthcare professionals are important pillars of the quality of the Dutch healthcare system. Scientific research in the UMCs contributes significantly to the quality and timeliness of medical education and training. The new generation of physicians will be responsible for the quality of life of millions of patients who, as a result of demographic change, will have a higher average age. These older patients will display more complex diseases and they will often suffer from multiple long-term conditions (multi-morbidity). The Netherlands Institute for Social Research has predicted that there will be about one million patients with multi-morbidity in the Netherlands by 2040. Furthermore, health is more than the absence of physical illnesses. Many conditions substantially affect the patient’s social and societal functioning. Chronic paediatric diseases also require special attention because they often result in life-long disability or impairment in social functioning. In addition to wider attention to the non-physical aspects of disease, the prevention of lifestyle-related diseases through better information about diet and lifestyle using new forms of knowledge transfer (i.e., health literacy) will gain importance in daily medical practice.

Future medical doctors should be prepared to use new technologies for early diagnosis, genetic analysis and the implementation of big data in medical practice, in order to achieve personalised medicine. Therefore, the UMCs, universities and training networks strive for excellence and continuous innovation, in all phases of medical training and in related education programmes such as biomedical sciences, health sciences, dentistry, biomedical technology, nanobiology, clinical technology and bioinformatics.

**SOCIAL RELEVANCE**

Public and political attention to the societal relevance of scientific research has grown in recent years. The KNAW discerns societal quality, impact and valorisation as components of societal relevance in its ‘Guide to the evaluation of societal relevance of scientific research’ (Eric-publication 1001, 2010). It is evident that the UMCs perform highly socially relevant work. For instance, the UMCs conduct a large number of accreditation audits every year to arrive at optimal, sensible and cost-effective healthcare. In addition, translating laboratory and clinical findings for the benefit of patients and the market are high on the UMCs’ agendas and these are considered core tasks. High-quality scientific knowledge is often also economically relevant. It is with good reason that the Dutch economy is increasingly referred to as a ‘knowledge economy’. The UMCs are involved in setting the agendas of the top sectors Life Sciences & Health, Agri & Food and High Tech Systems & Materials. Knowledge institutes like the UMCs have a societal responsibility to contribute to economically productive innovations. Economic exploitation is an excellent way to ensure that innovative knowledge is used to
the benefit of patients, in the form of improved prevention, diagnosis, or treatment. Naturally, the greatest care is taken to consider the possible tensions between commercial applications, science and clinical practice. To this end, the NFU has established guidelines (www.nfu.nl). Another example is the Innovative Medical Devices Initiative (www.IMDI.nl). In this initiative, research, care and industry join forces to enhance the sustainability of healthcare with new medical products, services and knowledge networks. From this starting point, the initiative aims to give impetus to the Dutch economy.

The UMCs have the expertise to identify interesting findings and to assist their employees in patenting these. These activities are organised in Technology Transfer Offices, often in collaboration with universities. The UMCs’ entrepreneurial climate is good, but there are still challenges to overcome. Entrepreneurship implies getting freedom and trust, taking calculated risks and showing courage. This requires a more active role of the UMCs, i.e., providing role models, sharing success stories and actively calling attention to entrepreneurship in education programmes. Each UMC applies the latter in its own way, especially within the PhD training programmes of the graduate schools. The UMCs are a great source of spin-outs; they strive to preserve and strengthen these spin-outs. Moreover, the UMCs currently are at the forefront of ongoing transitions in healthcare, e.g., the transition from classical drugs to ‘biologicals’, the step towards personalised medicine, to self-management through e-health, the potential of regenerative medicine and genomics, and of techniques for early disease detection using biomarkers. Finally, the UMCs critically evaluate the added value and cost-effectiveness of innovations.
Sustainable health is a common objective, related to the eight UMCs’ societal task. Sustainable health entails keeping people healthy at reasonable cost. It is also about keeping our healthcare system accessible, affordable and high-quality. Collaboration of strategic partners such as healthcare organisations, insurance companies, public authorities, industry, healthcare professionals and citizens is essential to achieve a sustainable healthcare system. The complete chain from fundamental research to a more personalised approach of prevention and treatment, as well as the financial implications, will determine if we can bring the sustainable health goal closer. Recent scientific and technological developments offer great opportunities to force breakthroughs in the coming years. The Netherlands can make a major contribution to this. The most important themes that will play a crucial role in the development of a sustainable healthcare system in the coming years are listed below. They seamlessly fit into the routes of the Dutch National Science Agenda:

A Healthcare research, prevention and treatment
B Personalised medicine
C Regenerative medicine
D Big data and Data4lifesciences
E Large-scale research infrastructure
HEALTHCARE RESEARCH, PREVENTION AND TREATMENT

Disease prevention will experience an unprecedented development in the years to come. As a result, more attention will be given to public health, prevention, lifestyle and care, diagnostics in children and adolescents, and revalidation. Our future healthcare will increasingly rely on the identification and correct interpretation of the earliest signs of disease susceptibility, aimed at preventing disease and serious consequences on an individual basis. It will also focus on secondary prevention, i.e., preventing disease development after a successful treatment, for instance diabetes in cancer survivors. The goal is to identify innovative solutions. In addition, the goal is to explore how the population's healthy lifespan ('health span') can be extended or how chronically ill people can be helped to function sustainably independent. Insight in basic mechanisms of disease development is crucial. Therefore, research that provides this insight should be developed further. This includes improved insight in biological processes and the perturbations therein that cause disease. It also includes risk assessment and addressing disease causes, such as genetic predisposition and exposure to adverse factors (e.g., food) which may give rise to changes in health status. Imaging techniques are crucial for medical doctors and scientists to understand health and disease at the molecular, cellular and organ level. Biobanks (especially for population research) can provide essential data for very early diagnostics. They can also provide clues on how to prevent people from falling ill.

Healthcare consumers themselves will contribute to these developments through e-health and m-health applications, which will be crucial to achieve sustainable health. Efficiently deploying available opportunities and actively involving the public, patients, the healthcare sector and the social sector will open avenues towards a sustainable healthcare system. In this respect, it will be crucial to evaluate the ‘new ways’ and healthcare innovations, including both the ‘MedTech’ or ‘devices’ and other types of innovations, e.g., healthcare transitions, task rearrangements, e-health and apps. Evidence-based practise is the motto here.
Prevention

Many questions about prevention were submitted to the Dutch National Research Agenda. These have been clustered in the route ‘Healthcare research, prevention and treatment’:

**PREVENTION**
How can we promote health and prevent disease through a healthy lifestyle and behaviour?

**SPORTS, EXERCISE AND NUTRITION**
How can we use sports, exercise and nutrition to promote good health and what will be the effects?

**OVERWEIGHT AND OBESITY**
How can we better understand and prevent the problem of overweight and obesity?

**DEGENERATION**
How does the central nervous system develop and how can we counteract neurodegeneration?
As an example. At present, the UMCs are conducting the following research in collaboration with other institutes and universities, to answer these questions.

**OBESITY AND LIFESTYLE**
Prevention of overweight and obesity is and will remain extremely relevant for children, adolescents, adults and elderly people alike. A large number of prevention programmes and guidelines have been developed in recent years, with a variety of prevention messages and target groups. However, these programmes have only very limited success. It is important to gain insight in the methods and conditions to change behaviour. Therefore, research on effective methods to influence lifestyle remains necessary.

**CARDIOVASCULAR DISEASE**
The underlying processes that lead to cardiovascular disease are increasingly well understood. It is possible to radically reduce morbidity and mortality from cardiovascular disease. One approach is early detection of risk factors before disease symptoms appear, followed by targeted interventions. Another approach is the implementation of genetic markers, improved cardiovascular imaging modalities (imaging markers) and new biomarkers in blood. This is being explored by the CVON consortia, among others. Research on individual risk factors will obtain a central position in the next few years. For instance, chronic kidney failure can cause cardiovascular problems, so research on biomarkers that can predict kidney damage is needed. Biobanks contain a wealth of information that can help understand mechanisms and define biomarkers. As a result, novel markers will be measured and individual treatments will be offered already at a young age (10-to-20-year olds).

**ONCOLOGY**
The Netherlands makes an important contribution to international cancer research, in the area of diagnostics and treatment, as well as in more basic cancer research. Cancer is the result of an interaction between congenital risk factors, lifestyle and environmental exposures. The appearance of a tumour is preceded by many years of gradual derailment. As with cardiovascular disease, in the future, individuals will be able to receive personalised advice to reduce their cancer risk. If someone develops cancer, more insight in risk factors, familial factors and possibilities for early diagnosis can be lifesaving. This is because curing cancer is mainly possible when the tumour can be completely removed at an early stage. In this way, the growing scientific knowledge can strongly reduce the individual and societal burden of cancer.

**NEUROLOGICAL DISORDERS**
The number of patients with a neurodegenerative disease is increasing as a result of population ageing. Neural decline is a gradual process that is increasingly understood. Interventions will be most successful when started early in this process. Therefore, it is of great importance to find new methods to detect a decline in brain functioning at an early stage. For instance, scientists are currently searching for indicators that can predict Alzheimer’s before a severe decline in daily functioning arises.

**PSYCHIATRIC DISORDERS**
Psychosis, depression, panic disorders and compulsive disorders can be treated effectively. Nevertheless, a major improvement has not yet occurred in the field of psychiatric disorders. One of the reasons for this lack of progress is the fact that psychiatric patients are often treated at a relatively
late stage. This is undesirable because chronic psychiatric disorders are associated with high societal dropout, somatic morbidity and premature mortality. Like the disciplines discussed above, psychiatry also strives towards earlier detection (e.g., in schizophrenia patients) and insight in the underlying pathophysiology (e.g., stress-related disorders). In addition, the field aims to offer the most appropriate preventive interventions or treatments much earlier, thereby preventing a first or next disease episode or chronicity.

**INFECTIONOUS DISEASES AND MEDICAL MICROBIOLOGY**

In addition to existing infectious diseases, so-called ‘emerging infections’ are manifest, e.g., Q fever, SARS and the MERS coronavirus. Some existing diseases are occurring more frequently, whether or not at epidemic levels (e.g., Ebola). The number of immunologically compromised elderly patients is increasing, partly as a result of population ageing. In this respect, the increase in antibiotic resistance is a worldwide concern: by 2050, the additional mortality due to un treatable infections may be higher than mortality from tumours if our antimicrobial resistance strategy is not changed. The spread of antimicrobial resistant microorganisms and multi-drug resistant organisms increasingly causes healthcare-associated infections (e.g., sepsis, postoperative wound infections, pneumonia and urine tract infections). Innovative research on the prevention of transmission and spreading, detection and new treatment modalities of multi-drug resistant organism infections will be key topics in the next few years. The development of ‘smart’ antibiotics and drug delivery systems that spare the healthy microbiome is relevant for the sustainable development of innovative drugs. The human, veterinary and environmental sector are all involved in the aetiology and spread of antimicrobial resistance, making a OneHealth approach necessary.
Personalised medicine

Personalised medicine tailors treatments to individual patient characteristics. Every person is unique, not only in behaviour and appearance, but also in body composition. Therefore, the same drug may have different effects in different patients. Personalised medicine facilitates a better, faster and cheaper treatment of diseases (NWO, 2011).
PERSONALISED MEDICINE

At present, steps are taken to individualise medical treatments, aimed at the largest and fastest health effects at the lowest cost, i.e., treatments tailored to the individual with as little undesired side-effects as possible rather than standard treatments. Personalised medicine will radically revolutionise healthcare: improved, personalised treatments associated with cost reduction. Biobanks offer unprecedented opportunities to develop better diagnostics, treatments and cures. The biggest challenge in personalised medicine is the analysis of the vast amount of data that is or will be produced by each individual and its correlation with disease parameters. This includes genome sequencing, microbiome studies, biomarkers in blood, and imaging in psychiatry, oncology, cardiovascular disease, diabetes, obesity and neurological diseases.

It concerns the complete cascade: from genetic factors, through a variety of factors and omics that play a role in the end phase where proteins and peptides exert their effects, to the daily functioning of patients. Other challenges are ageing, multimorbidity, the step to implement personalised medicine in clinical practice and to anchor it in the reimbursement system of health insurers.

The Netherlands holds a strong position in the area of personalised medicine the international LSH sector. The sector offers great opportunities to the Dutch knowledge economy because of its unique combination of knowledge and skills. The Dutch universities, knowledge institutes and scientific institutes are strategically well-positioned to make fast and efficient progress. Biobanks collaborate closely within BBMRI-NL2.0. In addition, there are multiple collaborations between the UMCs and the Hubrecht Institute to develop technical applications such as ‘organs-on-a-chip’. New opportunities for public-private partnerships are waiting. Large technology companies such as Philips and IBM are focusing increasingly on healthcare technology.

The same applies to data giants like Google and Microsoft. Crossovers are emerging between the top sector Life Sciences & Health and the top sector High Tech Systems & Materials. Joint agenda setting involving all stakeholders is needed to maximize the opportunities and benefits for patients.

Multiple developments are necessary for personalised medicine to deliver on its promise. First, it is important to actively involve patients, patient organisations and healthcare professionals in the development. Second, various types of research methods should be linked, e.g., imaging and metabolomics. In addition, the way to new preventive treatments and products will be opened by the link with technological innovations and building an IT infrastructure that makes existing resources accessible and interpretable for stakeholders. This is currently realised through Data4lifesciences in collaboration with BBMRI2.0, DTL and EATRIS.
Personalised medicine

Many questions about personalised medicine were submitted to the Dutch National Research Agenda. Examples are:

**BIOMARKERS**
How can we personalise healthcare, for example by using biomarkers?

**CARDIOVASCULAR DISEASE**
How can we predict, prevent and treat cardiovascular disease (atherosclerosis, heart failure, heart arrhythmia and thrombosis) at an early stage and at an individual level?

**GENETICS**
How will the knowledge of genetics be implemented in screening for and treatment of common and rare diseases?

**TUMOURS**
Every tumour is different, so how can we come to understand cancer well enough to develop a treatment for each and any type?
As an example. At present, the UMCs are conducting the following research in collaboration with other institutes and universities, to answer these questions.

**ONCOLOGY**
Oncology is one of the medical disciplines in which personalised medicine is already applied frequently in diagnostics and treatment. It has become increasingly clear why a standard cancer treatment does not produce the same result in all patients. The genetic composition of a tumour determines the success of a treatment. More techniques are becoming available to identify complex tumour characteristics, at the level of tumour biopsies (DNA and RNA analyses), blood (measuring markers), and tumour lesions (molecular imaging). Targeted cancer drugs exist; these target a specific molecular mechanism in a specific patient. It becomes increasingly possible to identify subgroups of patients that are highly likely to benefit from a specific treatment. Patients that are not expected to benefit from a certain drug will not receive the treatment; this spares them from unnecessary side-effects and it saves costs. Immune therapy is an approach that is currently showing impressive effects. This therapy triggers the patient’s immune system to attack cancer cells. Experts predict that at least half of all cancer treatments will consist of immune therapy ten years from now. A large number of new drugs that act via the immune system are in development. These drugs are often produced using the patient’s own body cells. However, scientists have not yet found a good method to identify patients that are likely to benefit from immune therapy.

**CARDIOVASCULAR DISEASE**
Premature mortality due to cardiovascular disease has been strongly reduced in the past few decades. Nevertheless, there is still a lot to improve in diagnostics, treatment and secondary prevention of cardiovascular disease. This is of extra importance because of the rising prevalence of chronic cardiovascular disease (e.g., heart failure) as a result of improved healthcare and ageing of the population. The exponential increase in knowledge about the biology, physiology and pathology of the complex cellular processes in vessel walls and cardiac muscle facilitates new risk stratifications and therapies. Gene therapy is being developed. Genetic modifiers, imaging of heart dysfunction and new biomarkers in blood will improve diagnostic and treatment strategies for heart muscle disorders. Pharmacogenetics should result in risk stratification and therapy that are optimised for the individual patient. A multidisciplinary approach with integration from bench to bedside (i.e., translational) is a first prerequisite for an effective implementation and evaluation of new concepts and therapies.

**PSYCHIATRIC DISORDERS**
Research in the past decade (e.g., within the national programme ‘MindPower’ (in Dutch: ‘GeestKracht’) has led to a substantial increase in knowledge about risk factors, individual symptom development, therapeutic relationship, aetiology, gene-environment interactions and disease pathways of psychiatric disorders. The combination of factors that leads to disease is unique to each patient. Therefore, a ‘one size fits all’ approach is not sufficient. There are opportunities for more personalised and – as a result- more precise and effective treatment in psychiatry as well, i.e., personalised mental healthcare. This requires a better knowledge of the underlying disease processes, the transitions between disease stages,
the overlap and differences between disorders, the aetiology of symptom-symptom associations and the factors that determine the creation of an adequate therapeutic relationship.

LUNG DISEASES
Lung research is focused on pulmonary P4 medicine (preventive, predictive, personalised, participatory). Treatment is thereby not only focused on specific patient characteristics (scientific perspective), but also on the patient’s specific needs (patient’s perspective). We need a better understanding of the processes underlying lung diseases (i.e., better phenotyping) in order to implement P4 medicine. In addition, lung research is increasingly focused on common mechanisms underlying different diseases, rather than disease-specific mechanisms. This calls for a broad and multi-disciplinary approach that transcends diseases. Big data analysis of existing and new databases creates opportunities to detect previously unknown mechanisms. The same holds for creating a ‘virtual biobank lung diseases’ through frequent sampling of lifestyle, personal and disease characteristics. This may result in stratification of the individual health risk with tailored diagnostic and therapeutic interventions. For instance, lung treatment with e-health and e-monitoring based on phenotype (e.g., biomarker) can prevent undesired side-effects (i.e., precision management).

INFECTION AND IMMUNITY
In the next few years, antimicrobial therapy research will focus on optimising antibiotic therapy, developing alternative treatments, using biomarkers and developing modern diagnostics such as molecular diagnostics for both bacteria and biomarkers. In addition, researchers will focus on developing point-of-care tests to characterise bacteria, viruses and host responses. A more holistic approach to infectious diseases uses genetic markers, personal microbiome analysis and monitoring of interventions. This will result in new insights and therapeutic strategies with or without the use of antibiotics. Immunological research has made great progress in recent decades and the Netherlands has played a prominent role in this. The host defence against infectious diseases is increasingly well understood. In addition, it is more and more clear how genetic and environmental factors determine individual differences in host defence. This knowledge has successfully been applied to more effectively treat a derailed immune response (e.g., in the common disease rheumatoid arthritis).

RARE DISEASES
By definition, the number of patients suffering from a specific rare disease is small. However, the total number of rare diseases is substantial, and as a result, the total number of patients suffering from a rare disease is also substantial. Large steps have been taken in the area of rare disease therapy in the last few years. The Dutch Ministry of Health, Welfare and Sport has appointed Dutch and European centres of expertise for rare diseases, giving additional impetus to research on rare disease treatment. Patients and patient organisations are important partners in diagnosing and treating rare congenital disorders that manifest immediately after birth (e.g., PKU, cystic fibrosis) and rare diseases that manifest in adults (e.g., ALS). Patients are organising themselves more and more, for example through websites such as PatientsLikeMe (patientslikeme.com). Patient experiences and expertise are increasingly incorporated in scientific research.
REGENERATIVE MEDICINE

Regenerative medicine or replacement medicine entails regeneration of cells, tissues and even organs. Regenerative medicine utilises the body’s own material (e.g., stem cells or heart cells) to prevent or cure disease. Regenerative therapies have already been used in early clinical tests and in laboratory settings, e.g., to treat broken bones, cartilage defects, severe pressure ulcers, burns, blindness, deafness, heart damage, nerve damage, Parkinson’s disease, metastatic cancer and disorders of the liver, kidneys, heart and lungs. Regenerative medicine will possibly lead to life extension, because it allows for repairing damage caused by ageing. It is a multidisciplinary field, particularly in the area of chronic diseases. This is demonstrated by the following examples: cartilage cell therapy for the treatment of osteoarthritis, beta cell therapy for the treatment of diabetes, cardiac progenitor therapy for the treatment of heart failure, and bioengineering and mesenchymal stem cell therapy for the treatment of renal failure.

It is expected that regenerative medicine will be the starting point for many new types of medical treatment. Since regenerative medicine represents an emerging multidisciplinary field of research and clinical application, new insights into scientific issues, new partnerships and new educational and financing facilities are needed before this ‘new’ medicine will become beneficial.

We need insight in the complexity of tissues to be able to regenerate them. Isolation, differentiation and proliferation of stem cells are critical factors here. In addition, a better understanding of the cellular response in the tissue environment and the interaction between materials and this tissue environment is of great importance for the further development of regenerative medicine. Knowledge of the extracellular matrix is a major inspiration here.

Supporting technologies are required to perform efficacy and safety studies in addition to basic science. Examples of such technologies are biomarkers, imaging techniques, high-throughput technologies, in vitro and in vivo model systems, bioreactors and minimally invasive administration tools.

The development of new and adaptation of existing technologies involves high costs. Priority should be given to sustainably closing the knowledge gaps in basic research and enabling the development of expensive supporting technology (KNAW, 2010).

In regenerative medicine, fundamental disciplines (e.g., cell biology, materials science and chemistry) collaborate with more applied disciplines such as cell therapy and implantation technology. Involvement of social science disciplines such as law and ethics are important for a strong public support.
Regenerative disease

Questions about regenerative medicine submitted to the Dutch National Research Agenda:

KIDNEY DISEASE
What causes chronic kidney disease and how can it be detected sooner and then treated on an individual basis? Is an implantable artificial kidney feasible?

LUNG DISEASES
How can we improve our understanding and treatment of lung diseases? How can we let lungs regenerate?

STEM CELLS
How can we use cells, stem cells and biomaterials to engineer and regenerate tissues and organs?
As an example. At present, the UMCs are conducting the following research in collaboration with other institutes and universities, to answer these questions.

NEUROLOGICAL DISORDERS
Brain-on-a-chip is an important and promising new research technique where brain tissue is reconstructed using stem cell techniques. This can then be used for research in realistic models, e.g., to test drugs. At present, the field is working at the level of stem cells or organoids, but this will expand rapidly as a result of the collaboration between fundamental cell biologists, clinicians and pharmacologists. Related to this, research on stem cell therapy is also important. This research requires specific safety measures and the technology is expensive.

TRANSPLANTATION MEDICINE
The Netherlands plays a pioneering role in the field of transplantation medicine. Various innovations that have significantly increased the global survival of transplanted patients in recent decades have been realised within the Dutch UMCs. The development of organ perfusion technology is a new step that should help solve the enormous problem of long waiting times. This technology can repair ('regenerate') organs that were disapproved for transplantation, rendering them usable. Dedicated machines ‘resuscitate’ organs, allowing damaged lungs, livers and kidneys to recover. In addition, organs can be kept for longer, allowing more time to find a suitable ‘match’.
Data infrastructure

A data infrastructure is a generic solution for a specific aspect of scientific data handling, intended to lighten the load of researchers. It enables researchers to make optimal use of the diverse possibilities of IT technology. An infrastructure can take many forms: it may comprise an online catalogue of samples in a biobank, a standard method with which data in an electronic health record is made available, privacy regulations, the way in which IT is organised at UMCs, a data stewardship manual (HANDS, see www.data4lifesciences.nl), a generic way to exchange data or an expert who supports a researcher with data issues.
The UMCs offer an infrastructure that is very suitable for research by combining academic hospitals with associated medical faculties. The Netherlands is strongly positioned in the field of (medical) big data. Collaboration between the UMCs has been strengthened in recent years. By collecting (clinical) data and biomaterials at NFU level and by pooling the available information and materials, advancements are made in science, the treatment of patients and product development. The latter is crucial for strengthening the economic position of the pharmaceutical and biotechnology industries in the Netherlands.

The high-quality infrastructure that is needed to meet the data requirements, transcends the competence of individual researchers and, increasingly also the competence of the individual UMCs. In 2013, the NFU started the Data4lifesciences programme (www.data4lifesciences.nl) with several partners (e.g., DTL, SURF, eScience Center, CIT). This programme aims to develop a strategy to establish a national data infrastructure for the Dutch life sciences.

The starting point of Data4lifesciences is that research data should be FAIR (Findable, Accessible, Interoperable and Reusable) and made available in a scalable, distributed environment. The computational capacity required to process the data should come from both national and UMC-associated computing facilities.

The Data4lifesciences programme is setting up an innovative research data infrastructure within, for, by and between the UMCs and their partners. Urgent reasons for adapting the current infrastructure are the upcoming EU privacy regulations, the implementation of new electronic health records, and more stringent requirements for the quality of data management and reusability of data by important research sponsors (e.g., NWO, ZonMw and KWF).

The envisaged high-quality data infrastructure Data4lifesciences is to deliver will consist not only of technical facilities (hard and software), but also systems and processes for quality assurance and the required expertise of researchers and administrators. Data4lifesciences ensures administrative coordination, connecting local facilities and expertise networks to national and international infrastructures and vice versa.
The technological revolution in genetics and imaging (e.g., MRI, CT), among other areas, have resulted in an explosive growth of research data. In addition, these data are also extremely complex. Moreover, personalised medicine research requires large cohorts (i.e., groups of patients with similar characteristics), e.g., all men born between 1940 and 1950. Such cohorts can only be compiled through collaboration. Researchers are thus confronted with much more complex data, but also with stringent requirements in terms of privacy, quality, management and data sharing.

The joint action of the UMCs strengthens their competitive position in Europe by connecting to relevant parts of the ESFRI Roadmap, including BBMRI2.0 and ELIXIR. The current data infrastructure provides a good starting position, but this position can only be maintained if the UMCs, their partners and the government persist in striving to keep the infrastructure up to date. This is a prerequisite to attract substantial sustainable funding, to take full advantage of new European programmes, and to retain the Netherlands’ leading position in European research. Moreover, European infrastructures play an increasingly important role in the acquisition of new resources. The UMCs and universities are responsible for the quality of research data and the care with which they are collected, stored, processed and archived. In addition, they are responsible for compliance with the relevant regulations on privacy protection and patient safety. A high-quality national infrastructure is thus required. Data4lifesciences will play an important role in this.

At present, the Dutch funding system for biobanks, cohorts and big data facilities is not organised optimally. State funding is insufficient and occasional impulses are rare and often marginal. That is alarming because these facilities are the rate-limiting-step for the speed and efficiency of Life Science & Health research in the Netherlands.
Many questions about big data were submitted to the Dutch National Research Agenda, including:

**BIG DATA**

How can big data and technological innovations (e-health) contribute to healthcare? Why is there so little research with already collected data in the Netherlands?

**INNOVATIVE TECHNOLOGY**

How can we utilise a greater understanding of life to identify new targets for molecular therapies, antibiotics and antivirals? How can we use the phenomenal increase in processing power (innovative technology) optimally for health and drug research?
As an example. At present, the UMCs are conducting the following research in collaboration with other institutes and universities, to answer these questions.

**BIOBANKING**

As part of NWO’s National Roadmap for Large-Scale Research Facilities programme, a plan has been created for a joint approach to biobanking. In addition to the eight UMCs, the National Institute for Public Health and the Environment (RIVM), Dutch Cancer Institute (NKI) and several universities participate in this plan. The Netherlands leads the way in this field and has collected many biobanks and cohorts. BBMRI-NL2.0 connects these, creating larger collections and new research opportunities. A point to consider here is the interoperability of data derived from different collections. BBMRI promotes such interoperability. BBMRI-NL2.0’s mission is to create the infrastructure necessary to realise a national biobank research facility, which will be invaluable for translational research. That implies linking additional types of research material such as imaging and metabolomics, involving societal stakeholders such as patient organisations much more directly, and building the IT infrastructure that makes existing resources accessible and interpretable for all stakeholders, such as the catalogue of biobanks.

**INFECTIOUS DISEASES**

Serious infectious diseases are associated with an impaired immune response, involving factors such as pathogen virulence, genetic factors, epigenetic factors, chronic co-morbidity of the patient, as well as the type of immune response. Research on the complex interaction between pathogen and host requires proper clinical documenting, and biobanking of pathogens and patient material. Prominent examples in the field of infectious diseases are sepsis and meningitis. In recent years, substantial investments have been made in systems biology analysis of pathogen and host factors in order to use the new knowledge for the development of personalised medicine.

**ONCOLOGY**

Knowledge derived from biobanks is essential for further progress in the prevention and treatment of cancer. By collecting data from large numbers of patients and tumours, it will become clear which approach will be effective to treat tumours with specific characteristics. There are differences between patients. In addition, tumours evolve throughout the course of the disease. As a result, data from several sources are needed in addition to normal biopsies, e.g., molecular imaging, liquid biopsies and other biomarkers in blood. In combination with clinical data on treatment outcome, this produces a vast amount of information per patient. The next step is to summarise this data into clinically useful conclusions and to translate the findings into clinical decision tools. Here, the expertise of computational biologists and bioinformatics is indispensable. This is another area of increasing collaboration between UMCs, technical universities and universities.

**LUNG DISEASES**

Biobanks are essential in the process of research towards personalised medicine. Because of the scarcity of cells and tissues, a ‘virtual biobank for lung diseases’ should be set up, aiming for nationwide availability of biobank information for research, combined with appropriate clinical data.
BBMRI-NL

EPI12

BIOMATERIAL AND DATA COLLECTIONS

EATRIS

NeCEN

BIO IMAGING

ALL RESOURCES TO MEASURE
  e.g. genomics, transcriptomics, proteomics, metabolomics,
  bioimaging, microscopy, quantified self, lifestyle, nutritional
  studies

MCCA

MODEL SYSTEMS

DTL

Data4Lifesciences

INTERNATIONAL REFERENCE DATA

ALL RESOURCES FOR DATA STEWARDSHIP
  AND ANALYTICS: e.g. bioinformatics, informatics, biostatistics,
  computational (systems), biology, e-science, ICT, ...

RESEARCH PROJECT

RESEARCH OBJECTIVE

HEALTH

E-HEALTH & QUANTIFIED SELF DATA

INFORMATION & INSIGHT
The ambition and vision of the NFU is to establish a research infrastructure for personalised health and personalised medicine. The UMCs and their partners (universities, ministries, top sectors and private parties) aim to develop a national infrastructure for science and innovation projects, focused on personalised health (for citizens) and personalised medicine (for patients). A number of years ago, the NFU has joined forces with relevant stakeholders (ZonMw, ministries and top institutes) to establish a large infrastructure for the Life Sciences & Health domain.

It is clear that Life Science & Health research will be technology-driven and data-intensive in the near future. The economic and societal impact of the Dutch life sciences field is large, as is also evident from the large number of health-related questions submitted to the Dutch National Research Agenda. The importance of an excellent research infrastructure, which enables us to remain internationally competitive, is correspondingly large. NFU's ‘Committee on Research Infrastructures’ manages and prioritises in this process. Members of this committee include representatives of all UMCs, research infrastructures within the ESFRI roadmaps and national roadmaps, NKI-AVL, DTL and ZonMw. The committee actively engages with the relevant ministries and top sectors. This approach has already resulted in a focused NFU application in the Roadmap round 2014. The relationship with the ESFRI Roadmap was made explicit in the applications.

The figure on page 46 shows various components of life sciences research, related to the major research infrastructures in the current roadmap.

Funding should come from, inter alia, the investment grant NWO Large and NWO’s National Roadmap for Large-Scale Research Facilities programme. The European Strategy Forum on Research Infrastructures (ESFRI) is a key player that provides strategic advice on inter alia eight research infrastructures in the field of health (including BBMRI, ELIXIR and EATRIS). A national coordination team has been appointed to manage the entire spectrum of large infrastructures for the red life sciences. This team sets the life sciences investment agenda to maximise the return of scarce resources in the Netherlands: the goal is to effectively distribute money and to make more resources available for translational research. At present, the following major life sciences infrastructures are on the NWO roadmap.

**BBMRI-NL2.0:**
BBMRI-NL2.0 is the innovative integration of three complementary national infrastructures for personalised medicine: BBMRI-NL1.0 (biobanking), EPI2 (population imaging), and CTMM TraIT (IT for translational research). BBMRI-NL has been actively promoting and organising collaboration.
and standardisation between Dutch biobanks for more than six years. BBMRI-NL represents the Dutch biobanks, including PALGA (pathology consortium), large population cohorts (e.g., Lifelines, ERGO, NTR and LLLS), and clinical collections (e.g., String of Pearls Initiative, HEBON and KOALA). BBMRI-NL2.0 aims to bring together all relevant biomedical research infrastructures in a streamlined and efficient system.

**EATRIS:**
EATRIS aims to bridge the gap between medical scientific research and clinical application. This international collaboration is crucial for patients. It is important that European medical research safely and quickly finds its way to the patients who need it. EATRIS facilitates this process, focusing on translational research. More than 70 prominent academic institutes are involved in EATRIS. They make their knowledge, facilities and clinical research opportunities available to researchers. They come from Finland, Italy, Czech Republic, Denmark, France, Norway, Spain and the Netherlands.

**EPI2:**
The European Population Imaging Initiative (EPI2) is an infrastructure for large-scale imaging. It offers standardisation, protocols, centralised storage facilities, validated image analysis and biomarker reference databases for population and clinical imaging research. EPI2 is a part of BBMRI-NL2.0.

**NL-BIOIMAGING AM:**
NL-BiolImaging Advanced Microscopy (NL-BiolImaging AM) is a distributed advanced microscopy facility in the Netherlands. It boosts biomedical and life sciences research by providing access to state-of-the-art microscopy technologies that enable the direct visualization of dynamics of molecules and their interactions inside living cells and tissues. This information is essential for e.g. elucidating mechanisms of carcinogenesis, understanding the progression and molecular basis of neurodegenerative disorders like Alzheimer's disease, and for high-content drug screening. NL-BiolImaging AM is strongly connected to the eight UMCs in the Netherlands and to the ESFRI EuroBioImaging roadmap in Europe.

**NeCEN:**
Dutch electron microscopy is strong. Forces have been joined in the NeCEN consortium. The new cryo-electron microscope offers opportunities for pioneering research: it is possible to visualise three-dimensional macromolecular complexes, resulting in important information about the functioning of living cells. This opens up possibilities for many scientific fields where information on the structure of molecules is necessary for further development.

**Mouse Clinic for Cancer and Ageing (MCCA):**
The purpose of the MCCA is threefold. First, it provides researchers with mouse models for cancer and ageing, derived from several routinely used strains. Second, the MCCA is a biobank where a wide range of mice tissues are stored and made available to researchers. Third, the MCCA provides genetically modified mice (custom-made) to researchers who want to study ageing and cancer.
Advanced techniques: bio-imaging, microscopy and gentechology

Many questions about bio-imaging and microscopy were submitted to the Dutch National Research Agenda, including:

ADVANCED TECHNIQUES

how can we develop minimally invasive techniques and interventions for the diagnosis, prognosis and treatment of patients?

Can diseases such as dementia, cancer and cardiovascular disease be detected earlier and treated with high-tech diagnostic imaging techniques?

How can we incorporate the most advanced microscopy techniques in miniature tools for minimally invasive diagnosis and treatment of disease?
As an example. At present, the UMCs are conducting the following research in collaboration with other institutes and universities, to answer these questions.

ONCOLOGY
It is increasingly clear why a standard cancer treatment does not have the same effect in all patients. Scientific research has delivered the insight that the molecular characteristics of a tumour partly determine treatment success. More techniques are becoming available to map complex tumour characteristics, at the level of tumour biopsies (DNA and RNA analyses), blood (measuring markers), and tumour lesions (molecular imaging).

There are also important developments towards better tumour diagnostics, in order to be able to make the right choices for the best and most sparing surgery, radiotherapy and systemic therapy. It is expected that radiation oncologists and surgeons will increasingly be able to spare healthy tissue, partly as a result of more 3D-guided integrated radiotherapy, the developments of heavy particle radiation (protons) and minimal invasive surgery. It is expected that better prognostic markers will lead to less burdensome treatments.

NEUROLOGICAL DISORDERS
Cognitive decline is a common denominator of many neurological (neurodegenerative) as well as psychiatric disorders. The Netherlands is very strong in this type of research, in particular in applying innovative neuroimaging techniques. Imaging techniques can help reveal brain processes. National collaboration has a strong added value here.

GENOMICS
The opportunities for prevention and early treatment of disease increase with our increasing knowledge of the genome and the relationships between genes and diseases, partly as a result of biobanks. This will increase the average health level. The expected treatment response and susceptibility to side-effects can be established before the start of a therapy. In addition, new health promotion strategies become possible. This offers opportunities for more tailored treatment and prevention of diseases (personalised medicine). Eventually, it will be possible to offer preventive, diagnostic and therapeutic interventions tailored to the individual and his or her health risk profile, across the continuum from health to disease. For healthy individuals, this will involve lifestyle recommendations and other forms of prevention. For people with health problems, this will involve establishing specific subtypes of diseases, as well as targeted diagnostics and prognostics. For patients, it involves selecting medication and other therapy forms based on predicted responses (tailored drug treatment, pharmacogenetics). However, we are not there yet. It is necessary to invest in improving the quality and interpretation of genome sequencing data. In addition, we should invest in increasing our knowledge about genetic variation and improving medical professionals’ knowledge about genetics and Next Generation Sequencing (Health Council of the Netherlands, 2015). It is also important to preserve the concentration of clinical genetic care within the UMCs and to increase its capacity.
Genetics and tumours

Questions submitted to the Dutch National Research Agenda:

GENETICS
How will the knowledge of genetics be implemented in screening for and treatment of common and rare diseases?

81

TUMOURS
Each tumour is different, so how can we come to understand cancer well enough to develop a treatment for each and every type?

85
As an example. At present, the UMCs are conducting the following research in collaboration with other institutes and universities, to answer these questions.

CARDIOVASCULAR DISEASE
At present, research on basic cardiovascular processes needs an incentive. There is a need for good functional ‘read-outs’ to establish malfunctioning of vessels and the heart muscle. This is important in preventing morbidity, which will be increasingly important in the future. Therefore, research should focus on: personalised predictions, early detection, genomics, big data analysis for early diagnostics, pattern recognition, reliable prediction and targeted treatment. The early diagnostics and the translation to the individual level are the next steps to be taken.

RARE DISEASES
More and better diagnostic methods are developed. More research is needed on the implementation of new genetic techniques (including exome and genome sequencing) and in vitro models (such as stem cell organoids) into routine rare disease diagnostics. In addition, more research should be performed on the effects of the observed gene variants (using both bioinformatics and functional studies). These data should be published in global databases.
The NFU will use the following principles to guide its steps in the coming years, e.g., in the development of the Dutch National Research Agenda and Data4lifesciences, in the utilisation of resources from the National Roadmap for Large-Scale Research Facilities, in its involvement in the top sectors and the elaboration of the ‘2025 Vision for Science, choices for the future’.
INNOVATION THROUGH CONNECTION.
The innovation engine in the healthcare sector is fuelled by linking care, research and business. That is where opportunities and possibilities arise: in cross-pollination and smart, sometimes unexpected, connections.

STRENGTHENING EXCELLENCE.
Dutch medical science and health research is internationally leading in many areas.

FROM BASIC RESEARCH TO CLINICAL APPLICATION UNDER ONE ROOF.
The way in which UMCs are organised is unique in the world and enables a single institute to cover the whole spectrum from basic exploration, through translational research and patient-related research to clinical applications. Given the excellent cooperation between basic research and clinical research within the UMCs, the Netherlands is eminently able to translate research findings into the clinic.

MAKING KNOWLEDGE AVAILABLE WIDELY AND QUICKLY.
In the interest of patients, knowledge and expertise are shared, both within regional networks and between the UMCs.

INKING EDUCATION, RESEARCH, PATIENT CARE AND VALORISATION.
UMCs are healthcare institutions as well as research institutes. Moreover, they are an engine for healthcare innovation. They have a major economic impact through knowledge valorisation.

DEFINITION OF HEALTH ECONOMIC REGIONS AND BUDGETS,
where UMCs generate knowledge in the regional network and innovative companies generate capital from this knowledge, which in turn can partly flow in the regional knowledge cycle (knowledge innovation engine).

INCREASING EFFICIENCY THROUGH CONCENTRATION AND DIVISION OF LABOUR.
Concentration is required to effectively link basic and clinical research on rare diseases. Where relevant, partnerships are set up and cooperation is taking place.

COLLABORATION BETWEEN UMCs.
The UMCs depend increasingly on expensive infrastructure and are collaborating increasingly in this respect. The UMCs have also joined forces in the field of quality assurance. There is concerted action towards the national government and Europe in as many contexts as possible. In addition, the UMCs collaborate to promote Dutch medical knowledge and skills internationally.
STRATEGIC PARTNERSHIPS.
At present, medicine and healthcare are strongly stimulated by the basic sciences, such as biotechnology, molecular genetics and physics. Innovation and technology are indispensable to bring personalised health and medicine to maturity. Particular attention should be given to bioinformatics because of the large amounts of data produced by personalised health. Data management and analysis (big data), as well as tools to evaluate decisions and interventions are also essential here. Translating all new scientific insights into better prevention, diagnostics and treatment of diseases will be the grand challenge for the coming decades. To this end, new strategic partnerships are needed.

SYNERGY IS ACHIEVED
by being responsive, responding to initiatives in and from society, either from the national government or from the EU, international associations, industry, patient organisations or otherwise.

PROMOTION.
Optimal international positioning and striving for excellence in research requires image building and collaboration.
As an example. Several of the above principles entail collaboration. Hence, several examples of partnerships are described below.

**ONCOLOGY**

Cancer care is successful, but also complex, highly specialised and expensive. This calls for a different organisation of cancer care. To this end, the UMCs, NKI-AVL and the PMC follow the American example of Comprehensive Care Networks (CCN). This is in line with the Field Agenda Oncological Care, which was set by the NFU, NVZ, SAZ, STZ, IKNL, NFK and SONCOS, in which highly specialised oncology centres cooperate with other relevant care providers. In the Dutch counterpart of CCN, the UMCs and general hospitals have formed comprehensive regional care networks. The networks provide direction on cooperation in diagnostics and treatment and on contacts with health insurers and the government. The UMCs and NKI-AVL provide the networks with expert knowledge for optimal diagnostics and treatment, as well as a strong infrastructure for research and innovation. Care professionals within a network collaborate on various diagnostic groups, based on agreed protocols. In this way, the care for patients with specific forms of cancer is concentrated in a limited number of hospitals. As a result, cancer patients cannot be treated in every hospital, but they will get the best possible care.

**INFECTIOUS DISEASES AND MEDICAL MICROBIOLOGY**

At the European level, the consortium COMBACTE (Combatting Bacterial Resistance in Europe) is active under the banner of IMI (Innovative Medicine Initiative). The aim of this project is to accelerate antibiotic development by designing and implementing new ways to perform clinical trials. One of COMBACTE’s activities is the development of a European clinical trial network for studies of, for example, new antibiotics (CLIN-Net). In 2015, researchers from all UMCs expressed their intention to jointly set up clinical trials within the Dutch arm of CLIN-Net (SION: Foundation for Infectious Diseases Research Netherlands). In addition to COMBACTE, the Netherlands hosts several WHO collaborating centres in the field of infectious diseases. The Netherlands Center for OneHealth is another partnership in this area. In addition, there are major framework projects for infectious diseases and antibiotic resistance in the years 2015-2020. First, the JPI-AMR for research in Europe and the framework project
EU-Interreg-Va along the Dutch-Belgian and Dutch-German borders (deutschland-niederlande.eu). The topics ‘OneHealth’ and ‘epidemiology and control of antibiotic resistance’ have been explicitly mentioned as focus areas in the EU-Interreg-Va innovation programme. In the Dutch-Belgian border region, the project i-4-1-Health is active. In the Dutch-German border region, two projects are active: health-i-care (towards collaboration between knowledge institutes and SMEs) and EurHealth-1Health (towards collaboration between knowledge and care institutions and institutions in the human, veterinary and environmental sectors). Both projects aim to improve our control of infections and resistance. Furthermore, there are research projects on OneHealth and environmental antibiotic resistance in collaboration with the top sector Water and Water JPI.

NEUROLOGICAL AND PSYCHIATRIC DISORDERS
Since 2010, Dutch brain and cognition research has been organised in a national task force, the National Initiative Brain and Cognition (www.hersenenencognitie.nl). This umbrella organisation manages national initiatives in research, neuroimaging, fund raising, marketing and PR.

The initiative includes a dedicated program of NWO / ZonMw, the FES programme Brain & Cognition, several national coordination structures and a partnership in BBMRI-NL2.o. It is also an interlocutor of the top sectors. Taken together, the National Initiative Brain and Cognition has generated EUR 80 million for research, mainly through public-private partnerships.
The UMCs and the training regions make an important contribution to the future of Dutch healthcare through education and training. Future medical doctors are confronted with an increasingly elderly population, a changing palette of patients, application of technology in healthcare, medically literate patients and so-called global health issues. Prevention and early diagnostics play a more prominent role. Healthcare will increasingly deal with the entire life course, i.e., ‘healthy ageing starts at conception’. This calls for a different type of healthcare professional as well as adequate modern education, which remains attractive for future physicians and researchers. It requires anticipating now, to be able to deliver the right healthcare professional in the near future, also from the patient’s perspective.

The UMCs take care of the initial basic medical training and the continuous education of medical specialists. They also organise ongoing training activities for medical specialists and other healthcare professionals. The UMCs are crucial for training adequately qualified other healthcare professionals, and for the training of biomedical researchers.
Education and training serve patients and society and always go hand in hand with patient care and scientific research. New insights and knowledge from scientific research are disseminated through education and training. The UMCs collaborate at the regional level with general hospitals and other educational institutions (such as applied universities) in the Training and Education Regions.

The UMCs aim to ensure efficiency and continuity, realising the training of qualified healthcare professionals throughout their career and providing a complete learning environment. There is an intensive collaboration with the regional industry. Learning, innovation and marketing converge at the campuses. Naturally, there is a close relationship between medical education and the related education programmes such as biomedical sciences, biopharmacy, health sciences, dentistry, biomedical engineering, nanobiology, clinical technology and bioinformatics. Continuous innovation is also important within these programmes. Crossovers are increasingly occurring, starting from the complex societal issues that increasingly demand a multidisciplinary approach.

The interest in medical education exceeds the number of available places for students (2,850 study places). In 2015, selection at UMC level was implemented in all education programmes in anticipation of the introduction of selection instead of drawing lots in academic year 2017-2018. The UMCs will further refine their decentralised selection procedures in the next few years, partly based on research on the effects of selection. In the training profile, appropriate methods should contribute to the match between student and education. However, the success rate of students is already high and the UMCs attract many international and PhD students.

In 2012, the report ‘Medical Education in the Netherlands in 2012, State of the Art Report and Benchmark report of the review committee Medicine 2011/2012’ (QANU, Utrecht 2012) formulated future developments as follows: “It is evident that medical education will have a different appearance in the future than in past decades. Healthcare and the medical profession are changing rapidly.” This calls for, as the report indicates, more standardisation and individualisation instead of uniform paths for all students, more and better integration between basic subjects and the clinic, a stronger training in ‘habits of inquiry and improvement ‘ and professional education with a focus on ethics and professional values.

The UMCs aim to modernise their educational curriculum continuously and adapt it to the changing needs of society. The goal is to increase the quality and efficiency of healthcare, e.g., by offering more variety in training, in terms of content and duration. Each UMC does so in its own way. In addition, ‘éducation permanente’ is optimised, i.e., continuous education and training of healthcare professionals, including fellowships. The UMCs also study their own education programmes in order to pursue evidence-based education. This is a major strength of the UMCs and it will be a permanent priority. The challenges
for the future lie in strengthening the educational continuum, combining the professions of scientist and medical doctor, the multidisciplinary approach and a changing career path.

The future scenarios for education and training are as follows:

- The medical specialist advanced training will become more flexible and will adapt to changing demands (e.g., geriatrics);
- The medical specialist will increasingly be freed of simpler tasks, allowing him or her to focus on complex healthcare issues. The interaction with other professionals and patients will become increasingly important (in terms of file transfer, who does what, what are responsibilities and checks);
- Cost savings will be achieved due to decreased efforts spent by medical specialists on less complex healthcare issues and tasks;
- Discipline-transcending education will become more efficient because it will be spread across multiple disciplines;
- Students and researchers will be working in the context of international networks: Dutch students perform internships abroad and foreign students (both masters and PhD) come to the Netherlands for education and research;
- Students will have increasing opportunities to profile and differentiate at medical school.

By elaborating and implementing these future scenarios, the UMCs contribute to the debate on the future of healthcare in the Netherlands and worldwide, starting from the content of medical training, i.e., care that is delivered by motivated and skilled professionals, of excellent quality, and accessible and affordable for those who need it.

The Framework for Undergraduate Medical Education 2009 describes the collective national goals of initial medical training. Each UMC decides on its own road towards these goals and there is room for differentiation between UMCs, so students can make an informed choice for a certain training location. This unique concept bears fruit: evaluations and international comparisons show that the quality of Dutch medical training is high. New evaluations of our medical education programmes will take place in 2017. This will provide input for a new version of the Framework Medical Education, to be completed in 2019. This will cover at least the following topics: societal developments, changes in healthcare professions, the changing role of the doctor, the consequences of the increased use of new technologies and the growth of small-group teaching.
6 To conclude: the major challenge

This National Plan has addressed the Dutch UMCs’ central research themes: research on prevention, personalised medicine, regenerative medicine, the optimal use of big data through Data4lifesciences and a large-scale research infrastructure. New technologies, research and treatment strategies, such as regenerative medicine and genomics, require opportunities and investments. Biobanks, cohorts and big data facilities will constitute the ‘rate limiting step’ in the transition to sustainable health. Education will come along and it will ensure that future healthcare professionals are equipped for their jobs, along with patients and those around patients. The urgency to come up with a joint strategy to keep healthcare costs within limits in the long term is present more than ever.
This National Plan describes the UMCs’ course for the coming years. The themes will be taken up energetically and in accordance with the principles listed in chapter 4. Choices have to be made to make science the engine of sustainable and innovative healthcare. This applies to the NFU and the UMCs, but also to society and the partners of the UMCs.

The NFU will use the principles listed in chapter 4 to guide its steps in the coming years, e.g., in the development of the Dutch National Research Agenda and Data4lifesciences, in the utilisation of resources from the National Roadmap for Large-Scale Research Facilities, in its involvement in the top sectors and the elaboration of the Science vision.

**ELABORATION IN ROUTE WORKSHOPS**

In the shorter term, the Dutch National Research Agenda will play a special role in the elaboration of this National Plan. The UMCs will take the initiative to fill in the details for the themes of health research-prevention-treatment, personalised medicine and regenerative medicine, in collaboration with all stakeholders. To this end, the UMCs will organise ‘route workshops’ in the first half of 2016. These workshops aim to connect underlying complex issues and stakeholders and to forge new partnerships to further shape existing research agendas. In addition, the NFU will contribute to route workshops based on the themes of ‘big data and Data4lifesciences’ and ‘large-scale infrastructure’.

The described transition to sustainable health, prevention rather than care and more personalised medicine with ‘more impact, less burden’ requires joining forces. It also requires profiling of UMCs, universities and research institutions. It calls for a widely supported joint optimal strategy of all partners in healthcare, in order to deploy the available resources as efficiently and effectively as possible. This is the only way to realise sustainable health. In addition, this is the only way for Europe to keep performing above average and to keep excelling at the international top. It requires a concerted effort of all societal parties that have a role in sustainable health.
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NOWT (Netherlands Observatory of Science and Technology), 2010. Science and Technology Indicators (in Dutch).


## Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>CCN</td>
<td>Centers for Cardiology Netherlands</td>
</tr>
<tr>
<td>CIT</td>
<td>Center for Information Technology</td>
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<tr>
<td>DTL</td>
<td>Dutch Techcentre for Life Sciences</td>
</tr>
<tr>
<td>IKNL</td>
<td>Netherlands Comprehensive Cancer Organisation</td>
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<tr>
<td>KNAW</td>
<td>Royal Netherlands Academy of Arts and Sciences</td>
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<tr>
<td>KWF</td>
<td>Dutch Cancer Society (DCS)</td>
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<tr>
<td>MKB-Nederland</td>
<td>Royal Association MKB-Nederland</td>
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<tr>
<td>NFU</td>
<td>Netherlands Federation of University Medical Centers</td>
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<tr>
<td>NKI-AVL</td>
<td>Netherlands Cancer Institute - Antoni van Leeuwenhoek</td>
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<tr>
<td>NVZ</td>
<td>Dutch Hospital Association</td>
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<tr>
<td>NWO</td>
<td>Netherlands Organisation for Scientific Research</td>
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<tr>
<td>PMC</td>
<td>Paramedical centers</td>
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<tr>
<td>SAZ</td>
<td>Collaborative General Hospitals</td>
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<tr>
<td>SONCOS</td>
<td>Foundation for Collaboration in Oncology</td>
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<tr>
<td>STZ</td>
<td>Collaborative Topclinical training Hospitals</td>
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<tr>
<td>SURF</td>
<td>Collaborative organisation for ICT in Dutch higher education and research</td>
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<tr>
<td>TNO</td>
<td>Netherlands Organisation for applied scientific research</td>
</tr>
<tr>
<td>TO2</td>
<td>Federation of Institutes for applied research</td>
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<tr>
<td>UMC</td>
<td>University Medical Center</td>
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<tr>
<td>VH</td>
<td>Netherlands Association of Universities of Applied Sciences</td>
</tr>
<tr>
<td>VNO-NCW</td>
<td>Confederation of Netherlands Industry and Employers</td>
</tr>
<tr>
<td>VSNU</td>
<td>Association of research universities in the Netherlands</td>
</tr>
<tr>
<td>ZonMw</td>
<td>Netherlands Organisation for Health Research and Development</td>
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</table>
Until 1 May 2015, all Dutch citizens could submit their questions to science on the website wetenschapsagenda.nl. The questions have been assessed for usefulness to the Dutch National Research Agenda. In consultation with the stakeholders, they have been clustered in themes. The resulting agenda was launched in November 2015. The Dutch National Research Agenda seeks connections with existing research agendas such as the European Horizon2020 programme. In the short and medium term the Dutch National Research Agenda will be translated into the profiles of universities and universes of applied sciences, the programming of the knowledge coalition’s partners, the direction in which the national research institutes develop, and into investments in large-scale research facilities. See www.wetenschapsagenda.nl/national-science-agenda/?lang=en for more information.

‘Route workshops’ will take place in the first half of 2016. These workshops aim to connect underlying complex issues and stakeholders and to forge new partnerships to further shape existing research agendas.

In the Dutch top sector approach, industry, science and government work together to maintain sustainable economic growth and to tackle societal challenges. This unique form of collaboration is designed to promote innovation, to attract talents, and to ensure a solid position for the sectors in the international context. The top sector approach focuses on the nine sectors in which the Netherlands is a global leader. Please find more information on www.topsectoren.nl.

Dutch academic research funding can be roughly divided into three flows of funds. The first is state funding (i.e., direct government funding). The second flow of funds consists of funds from NWO and KNAW; these are awarded to specific research projects (i.e., indirect government funding). The third flow of consists of for instance contract research and ‘collecting box’ funds (i.e., contract research funding).

The Parelsnoer Institute (string of pearls) is a chain of biobanks where patient data and materials are collected for research into specific illnesses. By combining these data and materials from the UMCs, a biobank can offer unique opportunities for research into these illnesses, for improvement of patient care and for the development of new products. (www.parelsnoer.org)
Colophon

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