Every procedure in clinical practice and public health should take place on the basis of proof, rather than intuition or just ‘experience’. The mission of the Radboud Institute for Health Sciences (RIHS) is to improve clinical practice and public health by providing evidence about the efficacy and efficiency of existing and new tests, treatments and policies, by training young researchers in the methodology needed to obtain such evidence, and by developing new methodologies for more effective research in this field.

The starting point for research in the RIHS is a concrete medical or biomedical problem in clinical practice or public health for which a solution is required. Researchers working at the Institute typically investigate such problems through probabilistic studies among groups of (real or simulated) people. In line with the Radboudumc’s mission (‘to have a significant impact on healthcare’), the Institute tries to bridge the gap between science and society, e.g. by getting involved in developing and evaluating guidelines and protocols. Societal impact is at the core of the Institute’s ambitions.

The RIHS received accreditation from the Royal Netherlands Academy of Arts and Sciences (KNAW) in 2014. Research at Radboudumc is organized in 19 research themes. Four of these are supported exclusively by the Donders Centre for Neuroscience and one exclusively by the Radboud Institute for Molecular Life Sciences. Since very few RIHS researchers work on the theme ‘Cancer development and immune defence’, we report here on the remaining 13 themes.
Healthcare improvement science  
**Theme leader:** Prof. Pim Assendelft  
The focus of research is to study the structure, process and outcomes of healthcare, with the aim of improving performance and delivery of care. The primary concern is providing direct value for patients. A further aim is to develop efficient and effective research methods and designs. Studies include the context, facilitators and barriers within which improvements in care around patients can be achieved, throughout the transmural care chain.

Infectious diseases and host response  
**Theme leader:** Prof. Mihai Netea  
Infections are caused by viruses, bacteria, fungi, and parasites. The main aim within this theme is to better understand the interaction of the host immune system with pathogens by combining cutting-edge research in immunology, microbiology and systems biology with translational and implementation research. The ultimate goal is to identify personalized approaches to the diagnosis and treatment of patients with infections.

Inflammatory diseases  
**Theme leader:** Prof. Irma Joosten  
In the Western world chronic inflammation is among the leading causes of morbidity and mortality. This theme involves understanding and controlling inflammatory disease for the benefit of patients by i) unravelling the immune pathogenesis of inflammatory disease processes; ii) elucidating the role of tissue specific factors in the regulation of local immunity and inflammation; iii) identifying druggable targets and biomarkers; iv) developing clinical grading tools; and v) carrying out pharmacogenetic and epidemiological studies.

Mitochondrial diseases  
**Theme leader:** Prof. Jan Smeitink  
The mission within this theme is to better understand the cellular bioenergetics in health and disease at all levels of complexity. Knowledge thus gained will enable the development of preventive measures and make a substantial contribution to treatment strategies for mitochondrial diseases.

Poverty-related diseases  
**Theme leader:** Dr Teun Bousema  
Health can be improved worldwide through basic, clinical and translational research in poverty-related diseases. Researchers working on this theme aim to contribute to the academic development of professionals and institutes in the Netherlands as well as in low and middle-income countries. The aim is to understand the immunology, microbiology and systems biology of malaria, tuberculosis, HIV/AIDS and dengue, and to improve disease prevention and treatment, including the national health systems and health financing mechanisms in which they are embedded with translational and implementation research.
Rare cancers
**Theme leader:** Prof. Winette van der Graaf

Despite the rarity of each of the 186 ‘rare’ cancers (i.e. an incidence <6/100,000 per year), they represent in total about 22% of all cancer cases. They pose particular challenges due to their low frequency, including i) late or incorrect diagnosis; ii) lack of access to appropriate therapies and clinical expertise; iii) a very limited number of clinical trials due to the small number of patients; iv) lack of interest in developing new therapies due to market considerations; v) few available registries and tissue banks.

The aim is to improve diagnosis and prognosis for this patient group in a national and international collaborative setting.

Reconstructive and regenerative medicine
**Theme leader:** Prof. Wout Feitz

The focus within this theme is on the development and clinical translation of innovative diagnosis and therapies, including i) regenerative medicine and ii) nano-medicine, for personalized care and cure of patients needing reconstructions of lost or damaged tissues. This will be achieved by transdisciplinary research involving leading research groups in medicine, dentistry, biochemistry, chemistry, biology and materials science.

Renal disorders
**Theme leader:** Prof. Joost Hoenderop

Current and future care of patients with renal and renal-related disorders can be considerably improved. To achieve this, researchers working on this theme aim to i) increase knowledge of the molecular and immunological basis of rare glomerular and tubular disorders; ii) develop biomarkers for optimal prediction of outcome; and iii) apply strategies for preventing renal disease and improving renal replacement therapy.

Sensory disorders
**Theme leader:** Prof. Anneke den Hollander

The research focus here is to improve our understanding of the molecular mechanisms of retinal diseases, hearing impairment and deaf-blindness. By developing and improving diagnostic and predictive tests for sensory diseases, researchers working on this theme aim to bring new personalized rehabilitation strategies and therapies into the clinic, including gene therapy and retinal implants.

Tumours of the digestive tract
**Theme leader:** Prof. Iris Nagtegaal

The research done within this theme focuses on improving the prognosis and treatment of patients with tumours of the digestive tract, in particular colorectal and pancreatic cancer. Key objectives are i) developing diagnostic tools for staging and therapy response; and ii) innovation in surgical techniques and immunotherapy. Increasing knowledge of the aetiology, epidemiology and genetics of these tumours will improve cancer therapy in high-risk patients.

Urological cancers
**Theme leader:** Prof. Jack Schalken

Research involves identifying and evaluating the utility of new biomarkers and imaging techniques for risk, diagnostic, prognostic and predictive assessment in prostate, bladder and kidney cancer.

In addition, new and existing prevention and treatment modalities in these types of cancer are evaluated. Synergistic multidisciplinary research collaboration – from molecular life sciences to population sciences – ensures a focus on ‘utility’ for patients and for public health.

Vascular damage
**Theme leader:** Prof. Gerard Rongen

Primary prevention, early detection, and optimal treatment of atherosclerosis (to preserve end organ function) and implementation of effective diagnostics and therapies in practice are the key focus areas within this theme. The aim is to increase understanding of the causes and consequences of vascular injury and translate this knowledge into improved personalized cardiovascular healthcare.

Women’s cancers
**Theme leader:** Prof. Leon Massuger

The goal of this theme is to improve the patient-centred quality of care in women’s cancers (breast, ovary, cervix, vulva, endometrium as well as pregnancy-related cancer). This is done in partnership with patients through prevention, early diagnosis or implementation of new management strategies supported by a better understanding of carcinogenesis and tumour development, paying special attention to hereditary causes, preservation of fertility and post-treatment individualized care.

Research facilities

In the Radboudumc, many facilities for research are brought together in a platform of Technology Centers, which is coordinated by Prof. Alain van Gool (see www.radboudumc.nl/Research/TechnologyCenters). Examples include:

- The Radboudumc Biobank, which contains large databases and biobanks of general population samples (the Nijmegen Biomedical Study) and of specific patient groups (e.g. congenital malformations, cancer, rheumatoid arthritis and inflammatory bowel disease).
- A clinical trial center offering logistics and data management for adult and paediatric human intervention studies.
- Consultation facilities for biostatistics, health economics and research with electronic health records.
- The Minimal Invasive Technology expert Centre (MIteC) field lab, which is used to evaluate surgical innovations.

In addition to these technology centers, examples of RIHS research facilities are:

- Academic networks of GP practices (including the GP Continuous Morbidity Registration), nursing homes,
Dr Rob Baltussen – Associate Professor International Health Economics – received an NWO Vici grant to establish a team of researchers to work on the prevention and treatment of HIV infections in South Africa and Indonesia.

Institutions for people with an intellectual disability, municipality health services, care facilities for homeless people and dental care sites.

- The ‘Koploper programme’, a healthcare innovation in which professionals in primary care, public health, allied healthcare workers and the hospital jointly develop new approaches to prevention and care.
- A SYstematic Review Centre for Laboratory animal Experimentation (www.SYRCLE.nl).

Collaboration

Although several research lines in the RIHS play a leading role worldwide, the Institute as a whole is best known in the Netherlands. To secure a transition to a more international level, RIHS offers two junior researcher positions annually for projects proposed by an RIHS researcher, together with an international partner. Appointed PhD students will carry out at least one year of the research abroad. Furthermore, a researcher or teacher from abroad is annually honoured with the ‘Richard Grol Visiting Scientist Award’.

There are formal collaborations with the Universities of Twente, Eindhoven and Groningen for, e.g. MITEC. At the Institute level, there is a formal partnership in the KNAW-accredited research school CaRe, together with CAPHRI (UM), NIVEL and EMGO+ (VUmc).

The Institute has formal ties with the HAN University of Applied Sciences, specifically in nursing sciences, physical therapy and musculoskeletal and neurorehabilitation therapy, and with the Nederlands Paramedisch Instituut. The Institute is also a formal partner in ‘Sterker op eigen benen’, a consortium of five service providers for people with intellectual disabilities. Within the Academic Collaborative Centre AMPHI the Institute collaborates with seven Dutch Community Health Services (GGDs). RIHS has collaborated with the Comprehensive Cancer Centre the Netherlands (IKNL), the National Expert and Training Centre for Breast Cancer Screening (LRCB), the RIVM, NIVEL, and the Dutch Ministry of Public Health, Well-being and Sports (VWS) for many years.

The RIHS collaborates in research and/or faculty exchanges with more than 40 universities around the world and with the European Union/ECDC, the WHO, UNESCO, the Centre on Birth Defects and Developmental Disabilities, various Centres for Disease Control and Prevention, INSERM (Paris), several Cochrane Centres, the MRC in London and deCODE Genetics in Reykjavik, Iceland. Within the scope of the EU 7th Framework Programmes EuroTARGET, TICD, EU-WISE, TACTICS, TLEMsafe, the Institute collaborates with numerous public and private organizations.

Research results

In 2014 the graduate school of the Radboud Institute for Health Sciences obtained formal accreditation from the Royal Netherlands Academy of Arts and Sciences (KNAW), indicating that the PhD training and supervision as well as the organization meet all the necessary criteria.

Some examples of research highlights are listed below.

Healthcare improvement science

Dr René Melis showed that mental health-related symptoms are likely predictors of multimorbidity, suggesting a strong impact of mental disorders on the health of older people (Melis et al. PLoS One 2014).
Key publications


Infectious diseases and host response
Prof. Marlies Hulscher and colleagues showed that appropriate antibiotic use in patients with a complicated urinary tract infection reduces the length of hospital stays and thus improves patient outcome, while reducing healthcare costs (Spoorenberg et al. Clinical Infectious Diseases 2014).

Inflammatory diseases
From a study among >4,000 smokers with mild-to-moderate COPD Dr Tjard Schermer and colleagues concluded that sex and age should be taken into account when assessing airflow obstruction. This observation has contributed to changing the recommendation on how to diagnose airflow obstruction (Akkermans et al. The European Respiratory Journal 2014).

Mitochondrial diseases
Dr Chris Verhaak and colleagues published the results of a randomized controlled trial on the effects of an online outpatient clinic for adolescents with T1Diabetes called Sugarsquare, showing that it improves communication between adolescents and healthcare professionals as well as quality of life in patients (Boogerd et al. Pediatric Diabetes 2014).

Poverty-related diseases
A novel malaria drug combination was developed and tested that kills both malaria parasites and mosquitoes. A study by Dr Teun Bousema and colleagues showed that the combination of a standard antimalarial with the mosquitocidal drug ivermectin was safe and efficacious in malaria patients (Ouédraogo et al. Clinical Infectious Diseases 2014).

Dr Teun Bousema and co-workers reported the first ever dose-ranging trial of the transmission-blocking drug primaquine, showing that the WHO’s previous recommendation of 0.75mg/kg can be changed to 0.4mg/kg or lower without any effect on preventing malaria transmission and without safety concerns in individuals with G6PD deficiency (Eziefula et al. Lancet Infectious Diseases 2014).

Rare cancers
Dr Anne de Waal showed that re-excision of low-stage melanoma has little value (de Waal et al. Virchows Archiv 2014).

Prof. Hans Kaanders’ group reported that accelerated radiotherapy, combined with carbogen breathing and nicotineamide increases tumour control rates in anaemic head and neck cancer patients. This is the first report ever describing a method that can improve the currently dismal outcome of patients with neoplasia-associated anaemia (Janssens et al. Clinical Cancer Research 2014).
Key publications


Dissertations: 81
Scientific publications: 1980
Patents: 2
Reconstructive and regenerative medicine
The team led by Prof. Nico Verdonschot won the international Grand Challenge competition. This competition, which is sponsored by NIH, is a worldwide endeavour in which researchers are challenged to predict loads in the knee joint of a patient with a total knee replacement.

In an international collaboration between Dr Roeleveld’s group and researchers from Denmark, Sweden and the USA, several new genes were identified that increase the risk of hypospadias (Geller et al. Nat Genet. 2014).

Renal disorders
Prof. Luuk Hilbrands and colleagues presented the results of a large randomized clinical trial on the use of the anti-B-cell agent rituximab as induction therapy after renal transplantation. The study showed that rituximab has beneficial effects in sensitized patients (Joosten et al. Transplant immunology 2014).

Sensory disorders
Prof. Carel Hoyng participated in a research team that found that people who reported having allergies had a significantly reduced risk of developing age-related macular degeneration (AMD), the most common cause of vision loss in elderly (Ristau et al. Investigative Ophthalmology & Visual Science 2014).

Tumours of the digestive tract
Prof. Kampman’s team showed that intake of dietary B vitamins and methionine has no effect on the risk of colorectal cancer in patients with Lynch syndrome (Jung et al. Cancer Causes Control 2014).

Urological cancers
Maarten de Rooij and Prof. Jelle Barentsz were awarded the ‘Lauterbur Award’ for the best scientific MRI-related work at a conference in New Orleans. Their study shows the ability of multiparametric MRI and MR-guided biopsy to improve prostate cancer diagnosis and demonstrates that this MRI strategy appears to be cost-effective compared to standard care (de Rooij et al. European Urology 2014).

Prof. Bart Kiemeney and colleagues identified a new susceptibility locus for bladder cancer at chromosome 20p (Rafnar et al. Human Molecular Genetics 2014).

Anne Grotenhuis showed that the genetic risk markers for bladder cancer have little prognostic value for the disease (Grotenhuis et al. PLoS One 2014).

Vascular damage
The EU-funded Tailored Implementation in Chronic Diseases project, led by Prof. Michel Wensing, published, as first in the world, methodological studies of tailoring methods (Wensing et al. PLoS One 2014).

Dr Dick Thijssen has described – for the first time – that exercise training leads to responders and non-responders in terms of improvement of endothelial function and identified ‘success factors’ for improved endothelial function (Green et al. Journal of Applied Physiology 2014).

Thijssen’s group also showed that exercise training can normalize elevated levels of retrograde shear and that these changes are related to the sympathetic nervous system. (Scholten et al. American Journal of Physiology - Heart and Circulatory Physiology 2014).

Women’s cancers
Dr Mireille Broeders participated in the EUROSCREEN Working Group, which proposed a review of studies on breast cancer screening effectiveness (Paci et al. CEBP 2014).

Dr Ruud Bekkers and colleagues completed a large randomized controlled screening trial in 45,000 non-responders to cervical cancer screening (Verhoef et al. Lancet Oncology 2014).

Awards and acknowledgements
• Prof. Bart Kiemeney was listed in Thomson Reuters’ ‘The world’s most influential scientific minds 2014’ list.
• Prof. Maroeska Rovers was invited as visiting professor to give a Grand Round on evidence-based surgery at Oxford University.
• Dr Nynke Scherpbier received the ‘Heert Dokter’ award from The Dutch College of General Practitioners for her research paper on telenephrology.
• Dr Simone van der Burg was awarded the Dutch L’Oréal UNESCO Fellowship for Women in Science.
• Prof. Richard Grol received the prestigious Donabedian International Award for Leadership in Quality of Care.

Societal impact
Much RIHS research is immediately implemented in clinical care or public health. Achieving societal impact is, in fact, one of the main aims. Some highlights in 2014 were:
• Prof. David Burger was one of the authors of the International Antiviral Society’s HIV Treatment Guidelines 2014.
• Dr Lisette Schoonhoven chaired the group that launched international clinical practice guidelines for the prevention and treatment of pressure ulcer.
Broeders’ group will start a study on the acceptability of personalized care and patient-centred interventions. For example, Dr Mireille The focus of research will increasingly be on personalized health-as biobanks as well as in large national and international networks. The Institute will continue to invest in research facilities such

Future research
The Institute will continue to invest in research facilities such as biobanks as well as in large national and international networks. The focus of research will increasingly be on personalized health-care and patient-centred interventions. For example, Dr Mireille Broeders’ group will start a study on the acceptability of personalized risk-based approaches in breast cancer screening in collaboration with the Karolinska Institute and the University of Manchester. With a Kolff post-doc grant from the Dutch Kidney Foundation Dr Loes van der Zanden will develop prognostic models for hypoplasia and renal function.

The ageing of the Dutch population will present enormous quality and efficiency challenges in healthcare. Cost-effectiveness will be central to healthcare policy for the next few decades. Four research groups will perform research on healthcare costs and effectiveness with grants from the ZonMw programme ‘Doelmatigheids-Onderzoek’: Prof. Anne Speckens (Mindfulness training in ADHD), Dr Dirk Kunst (Diagnostic strategies in patients with asymme-trical hearing impairment or symptoms suspected of vestibular schwann-noma), Dr Nanda Lambregts-Rommelse (Restricted elimination diet in children with ADHD) and Dr Erwin van Geenen (Fluid hydration to prevent complications after Endoscopic Retrograde Cholangiopancreaticography).

Two RIHS researchers will extend their research with prestigious personal grants: Dr Rob Baltussen was awarded a NWO Vici grant for the project ‘Balancing efficiency, equity and feasibility in HIV treatment in South Africa’. Dr Teun Bousema received an ERC starting grant for the project ‘Commitment, maturation and infectivity of sexual stage malaria parasites’.

Prof. Barentsz and colleagues will investigate the value of multi-parametric MRI and MR-guided biopsies in the detection of significant prostate cancer with an Alpe d’HuZes grant. Other projects that received awards from the Dutch Cancer Society are: ‘Identification of germline mutations in extremely early-onset bladder cancer’ (Prof. Bart Kiemeney and Dr Sita Vermeulen), ‘Cancer Related Fatigue in Childhood Cancer Survivors’ (Dr Jacqueline Loonen), ‘Efficacy of FDG-PET in the Evaluation of Cytological indeterminate Thyroid Nodules prior to Surgery’ (Dr Dennis Vriens), ‘A randomized Phase II feasibility study on the treatment of early stage rectal cancer’ (Prof. Hans de Wilt), ‘The influence of the oral microbiome and salivary proteome on oral complications in hematopoietic stem cell recipients’ (Prof. Nicole Blijlevens), ‘Early tubectomy with delayed oophorectomy to improve quality of life as alternative for salpingo-oophorectomy in BRCA mutation carriers’ (Dr Rosella Hermens, Dr Joanne de Hullu) and ‘The effectiveness of blended therapy on psychological distress in colorectal cancer survivors’ (Prof. Judith Prins).

Early detection of breast cancer through screening and subsequent treatment improves outcomes. The group led by Dr Chris de Korte will work on improving 3D automated volumetric breast scanning (ABVS) with an STW Open Technology grant.

With an EU Innovative Medicines Initiative (IMI) grant Profs. Bart Jan Kullberg, Marlies Hulscher and Inge Gyssens and their research partners will develop new economic models to provide incentives
for antibiotic discovery and development activities while safeguarding the efficacy of antibiotics.

Prof. Maroeska Rovers is developing a methodology for the early integrative evaluation (efficacy, costs, value) of surgical innovations. This requires a paradigm shift from the traditional sequential processes: development, assessment and appraisal.

Prof. Gert Westert and colleagues will start the new 'Roadmap to de-implementing low-value services in Dutch hospital care', financed by the Citrien Fund (ZonMw). Prof. Westert leads the research group on behalf of the eight university medical centers that are involved.