TNO S&I
innovations for healthcare and sport

Let’s make human beings better
Preface

After a century of industrialization and materialization that has led the world to a considerable rise in living standard, the society seems to recognize that the time has come to focus technology more on personal values such as health and wellbeing. Not only for ethical reasons. The western economy has evolved into a very consumer-centric system where consumers drive the demand. With the upcoming living standard, consumers demand it all: housing, food, pleasure, comfort, mobility, connectivity, entertainment, spiritual enrichment and last but least health and sport. With focus on improving his performance and wellbeing, of course against affordable costs that fits the consumer budget. The credo “let’s make human beings better” will address the future consumer demand and will impact strongly the macro economic performance both by consumption as well as by productivity.

This document has been compiled in order to find answers on the following questions:
-how does the market for health and sport evolve
-what are the main market demands
-which technologies, or set of technologies, can fulfill these demands
-how can this be implemented, concepts
-what barriers need to be overcome

TNO Science & Industry
portal Medical and Sport
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3500 billion $ spending in Healthcare annually, sources Medistat

300 billion $ spending in medical equipment, sources Medistat

* Largely physician salaries and cost of hospitalization

Source: OECD, 2003


**Market analysis, trends and issues**

Healthcare is world largest service sector, growing from 8% to 10% GDP (Europe) in 2010. Per capita in US $ 5300 is spent on healthcare, in Europe $ 2500 annually. Hospitalisation costs are quite dominant: 62%. The healthcare market is estimated to 3500 mld $ (2005) whereas the sport market is estimated to a 1000 mld $ market worldwide. European countries spent nowadays about 8% of their GDP on health, in the US already 12%. The health expenditures increase more rapidly than the GDP’s.

<table>
<thead>
<tr>
<th><strong>Healthcare</strong> (mld $, annually)</th>
<th>expenditures</th>
<th>growth %</th>
<th>trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total healthcare</td>
<td>3500</td>
<td>5</td>
<td>acceptable cost with more elderly</td>
</tr>
<tr>
<td>Primary healthcare (hospitalisation, physicians)</td>
<td>2000</td>
<td>4</td>
<td>reduced hospitalisation time shifting to homecare</td>
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<tr>
<td>Pharmaceuticals</td>
<td>500</td>
<td>10</td>
<td>targeted drug release, nanomedicine</td>
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<td>Medical equipment &amp; devices</td>
<td>300</td>
<td>5</td>
<td>early diagnosis, imaging, biochips, non/minimal invasive treatment</td>
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<tr>
<td>Homecare</td>
<td>350</td>
<td>8</td>
<td>rapidly increasing elderly population telemonitoring</td>
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<tr>
<td>Healthcare IT</td>
<td>80</td>
<td>11</td>
<td>electronic patient and medical dossier genotyping, bioinformatics</td>
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<td>Public activities</td>
<td>150</td>
<td>3</td>
<td>prevention programs, sport promotion</td>
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<tr>
<td>R&amp;D</td>
<td>120</td>
<td>3</td>
<td>50% in pharmaceuticals</td>
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<tr>
<th><strong>Sport</strong> (mld $, annually)</th>
<th>expenditures</th>
<th>growth rate</th>
<th>trends</th>
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<tbody>
<tr>
<td>Total</td>
<td>1000</td>
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<td>link with health, fitness + wellbeing</td>
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<tr>
<td>Facilities / accomodation, training</td>
<td>800</td>
<td></td>
<td>optimizing training conditions</td>
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<tr>
<td>Equipment</td>
<td>100</td>
<td></td>
<td>telemonitoring, (bio) model based training</td>
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<td>Footwear</td>
<td>50</td>
<td></td>
<td>adaptive, custom fit</td>
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<td>Apparel</td>
<td>50</td>
<td></td>
<td>sensor integration</td>
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Elderly and Upper Middle-age Population
U.S., 1970-2050

Note: Data for 2010 – 2050 projections based on Census Bureau's "Middle Series" Scenario

Personal Health Expenditures on Select High-Cost Conditions - 2000

<table>
<thead>
<tr>
<th>Condition</th>
<th>Expenditure</th>
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<tr>
<td>Cardiovascular Disease</td>
<td>172.9</td>
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<tr>
<td>Mental Illness</td>
<td>138.2</td>
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<tr>
<td>Cancer</td>
<td>96.4</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>92.5</td>
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<tr>
<td>Falls</td>
<td>45.1</td>
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<tr>
<td>Arthritis</td>
<td>29.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>28.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.2</td>
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<tr>
<td>Parkinson's Disease</td>
<td>18.9</td>
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Trends

More elderly demanding care: in 2030 is 25% of our population is > 65 yrs (now 17%)

Reduction of hospitalisation time, need for high efficient, high throughput hospital or clinic
  o non or minimal invasive surgery
  o personalized medicine
  o telemedicine
  o after care via telemonitoring

Professional care shifts to homecare, need for efficient and professional homecare system
  o care via IP
  o diagnostic tools at the home
  o self diagnostics and self treatment and rehabilitation
  o telemonitoring

Cost reduction in healthcare system via:
  o health IT
    ▪ electronic patient dossier
    ▪ electronic medical dossier
    ▪ telemonitoring
  o early diagnosis and treatment
    ▪ molecular imaging
    ▪ point of care diagnostics, lab-on-chip
  o dedicated treatment of specific chronic diseases (cardiovascular, mental, cancer, Alzheimer etc)
    ▪ targeted drugrelease
    ▪ personalized medicine, genotyping of patients, bioinformatics
  o prevention programs, sport and health promotion

Towards a consumer centric system:
  o health shopping
  o personalized medicine
  o cosmetic surgery
  o sport & fitness, wellness

Cost containment
home hospitalization program

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<th>Home hospitalization</th>
<th>Usual care</th>
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<td>1255 €</td>
<td>2033 €</td>
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Issues and technologies

healthcare
- cost reduction
- personal care
- wellbeing
- human performance
- early diagnosis & cure
- stimulation
- condition monitoring
- training coaching

sport
- medical
- pharma
- revalidation
- home care
- fitness
- sport
- imaging
- personalized medicine
- tele care
- ict
- body function monitoring
- implants
- targeted drug delivery
- lab-on-chip
- wireless sensors, RFID
- non invasive surgery
- robotics
- tissue wound skin treatment
- nutraceuticals
Issues in Healthcare and Sport

Healthcare and sport share many technologies in view of repair and improving human performance. Technologies for both areas are very human centric and the technologies have to deal with the human biosystem in many aspects such as:

- biomechanics (physical performance, training)
- physiology (food, energy balance, temperature/climate, clothing)
- systems biology (health condition, disease management, treatment, cure)
- neurological system (brain function, alertness, awareness, memory)
- mental and social behavior (decision making)
- genetic predisposition (physical, mental, biological etc)

It also implies that technologies developed in one area, can be transferred and adapted to the area in many cases. However the conditions in healthcare and sport are quite different.

Healthcare
- cost reduction is major goal
- acceptable level of healthcare is to be maintained
- separate treatment of mental and physical diseases

Sport
- maximizing human performance
- focus on body performance in combination with equipment and accomadation
- mental condition very important enabler
- creating performance stimulating environment
Growing markets

**Health IT:** ICT is offering major opportunities in terms of efficiency, cost reduction and quality improvement in healthcare. Current developments cover:
- electronic patient and medical dossiers for having the right information on the right time and place, improving speed, costs and quality of healthcare
- patient empowerment: for better informed and motivated patients
- telemonitoring both in homecare and professional care
- telemedicine and telesurgery
- bio-informatics, genotyping of people for early screening, diagnosis and gene-specific medical treatment

**Nanomedicine:** discovery of new drugs is slowing down (less new molecules are found, approval costs sky high), pharma companies seek new, more effective drug release systems for their existing drugs and integrate more and more with equipment and devices manufacturers. Most promising and growing area is nanomedicine:
- **nano-diagnostics** >> € 250 million by 2006
- **nanoscale targeted drug delivery** >> € 70 billion by 2007
- **regenerative medicine** >> € 80-100 billion by 2010
- **molecular imaging** >> € 22 billion by 2015

**Homecare:** 70% of homecare is on elderly (>65 yr) with heart/vascular disease, diabetes, osteoarthritis, fractures. There are two reasons for expected high growth of homecare:
- demographic reasons: the elderly population rapidly increases for next coming years (in Europe from 17% to 25% in 2025)
- cost reduction in hospitalisation: reduced hospitalisation times will shift care from the hospital to the homecare situation

It is unclear how and when this emerging homemarket will drive innovations in terms of homecare diagnostics (lab-on-chip, dipstick), telemonitoring, robotics etc.

**Body repair**
Although high expectations exist for the future market in tissue engineering for body, skin and organ repair (tissue replacement or insitu repair), the main markets with considerable growth (5-10%) for the next coming years are in:
- **Dental** € 100 billion
- **Cosmetic/plastic surgery** € 35 billion (surgery € 25 billion, non surgery € 10 billion)
- **Other implants** € 30 billion (pacemakers € 10 billion, stents € 10 billion, other e.g. hips+knee+cochlear € 10 billion)
Current technology issues health companies in NL

**Biocompatible coatings**

**Targeted drug release**

**Biocompatible coatings**

*Micro X-ray for brachytherapy*
*Micro ultrasound transducers*
*Focused ultrasound*

**Targeted drug release, release on demand**
*Alternative drug release systems*
*Anti counterfeit*

*Nanodispersion, solubility, drug delivery*

*Molecular medicine, focused ultrasound*
*Babycare, skincare, fitness, homecare*

*High performance materials, coatings for medical*
*Rapid manufacturing*

*Intelligent textile, sensor integration*

*Contamination control, coatings, 3D scanning*
*Biomechanical modelling, packaging*
Industrial playing field in the Netherlands: Health

Major health companies involved in health(care) in the Netherlands:

**Philips**
Philips Medical Systems (9 billion €): monitoring & imaging: ECG, MRI, CT, PET, X-ray, US - defibrillators
-health IT: medical lab IT, clinical IT, telemonitoring
Philips DAP (2 billion €): devices for consumer health & wellness (starting up)

**Medtronic** (10 billion $): pacemakers, cardiac surgery, vascular therapy (stents, catheters) -lifelong solutions for chronic diseases - surgery: cardiac/neurological/spinal/oncology/ENT surgery -diabetes, insulin pumps, glucose monitoring

**Solvay Pharmaceuticals Group** (2,5 billion €): hormone therapies, digestives/enzymes, influenza, antispasmodics, vertigo, alzheimer

**Organon** (2 billion €)
-pharmaceuticals: contraception, hormone therapy, fertility, mental health, and anaesthesia.

**Janssen Pharmaca** (2 billion €)
-pharmaceuticals for mental illness, neurological disorders, anaesthesia and analgesia, gastrointestinal disorders, fungal infection, allergies and cancer.

**DSM**: performance materials (2 billion €), Dyneema for medical, Solutech for sport clothing

**Cordis** (1 billion $): vascular disease management, stents, catheters

**Ten Cate** (600 million €): textile and fabrics for advanced clothing and sport (playing fields)

**Delft instruments**
Nucletron (100 million €)     Oldelft (12 million €)     Delft diagnostic imaging (18 million €)
-radiotherapy, brachytherapy  -ultrasound  -Xray diagnostics

**Mentor Medical** (500 million $)
-cosmetic implants, tissue expanders, aesthetic medicine, brachytherapy, personal care
Current technology issues in Sport in NL

Focus areas:
1. Training
devices and systems for performance monitoring and enhancement
2. Equipment, footwear & apparel
high performance equipment and clothing
3. Accommodations
performance stimulating environment
4. Food
food engineering
5. Sport stimulation
innovative approaches for sport stimulation
6. Human factors
technology integration with a high level of human acceptance

Maximizing performance
Innovation oriented
Field labs
Specialties
Injury management
Marketing & branding

Consumer market
Larger volumes
Fitness & wellbeing
Relation with healthcare
Activity incentives
External motivators

Top sport
Consumer sport
Wellness

Voeding
Sportstimulering
Sportmaterialen
Voedingssupplementen
Biomarkers
Devices for performance monitoring
Performance monitoring
Ondergronden
Multifunctioneel gebruik
Training
accommodaties

Asics
Philips
DSM
Jansen • fritsen
Polar
Suunto
NDC • NSF Top sport
Sponsoring logos
### Industrial playing field in the Netherlands: Sport

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<tr>
<th>Organisation</th>
<th>Focus area</th>
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</thead>
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<tr>
<td>Philips</td>
<td>Performance monitoring, electronics in clothing</td>
</tr>
<tr>
<td>Ten Cate</td>
<td>Textiles, accommodations (floor), equipment</td>
</tr>
<tr>
<td>DSM materials</td>
<td>Equipment and clothing, accommodations</td>
</tr>
<tr>
<td>DSM food specialties &amp; ingredients</td>
<td>Food engineering</td>
</tr>
<tr>
<td>Decathlon</td>
<td>Performance monitoring, equipment and clothing</td>
</tr>
<tr>
<td>Media (NOB, Talpa, Versatel,...)</td>
<td>Monitoring, more information to the consumer</td>
</tr>
<tr>
<td>Reebok, Adidas, Asics or Nike</td>
<td>Monitoring, equipment, clothing, footwear</td>
</tr>
<tr>
<td>CVZ, Achmea, DSW etc</td>
<td>Sport stimulation</td>
</tr>
</tbody>
</table>

![Diagram of Business Creatie and Acceleratie](image)
HEALTH CARE

- Less hospitalisation
- Homecare
- Elderly population
- Health IT
- Telemedicine
- Early diagnosis
- Drugs on target
- Minimal invasive
- Body repair & beauty
- Nanobio fusion
Nano for human health and wellbeing

Human centric systems are in development in order to secure and optimize human performance and well-being. The systems provide monitoring and feedback functions of the human being in its environment plus protection and support tools. This approach is seen in top sport, medical care, revalidation, first responders, firefighters, police and the military. In practice such systems result in the ability to participate in a mobile information network, use of more comfortable, protective and functional suits, wearable intelligence such as sensors and displays for situational awareness and body condition monitoring. Nanotechnology is here crucial. Without miniaturization such functionalities can not be adapted to lightweight, wearable systems.

Materials: nanotechnology enables high strength, durable, sensoric and active materials. Nanostructures and nanocomposites are in development for the following functionalities:
- lightweight protective clothes: against heavy injuries, supportive
- adaptive suit: switchable fabric for improved thermal control, switchable functionality
- microsensors for body & brain sensing, environmental and situational awareness
- wearable and/or flexible displays for visual feedback
- auxiliary supports: flexible/rigid textiles for additional strength, exoskeletons and robotics to assist tasks

Information: in order to operate in a safe and secure wireless network, the human will be equipped with:
- miniaturized hardware: sensors, readers, displays and radio transmitters, some of this already present in pda’s and mobile phones
- personal secured access to equipment (biometric id) and information (digital id)

Energy: with the increase in wearable functionalities and electronics, the need for lightweight wearable electric power is very critical. The following developments are present:
- flexible solar cells to recharge batteries
- μ-fuel cell, preferentially to be operated by diesel or biofuel (e.g. sugar)
- μ-nuclear battery for long endurance
- energy scavengers, e.g. electricity from vibrations, for low power applications

Bio: the nano-bio fusion is a booming area with high expectations that major steps in health treatment, body repair and body improvement can be made. It is regarded as the most innovative domain of this moment. Developments are in the field of:
- nanomedicine: targeted drug delivery by medically functionalized nanoparticles, for rapid cure without side effects or human stimulation
- regenerative medicine: DNA programmed tissue engineering for quick and efficient wound healing, rebuilt of organs and other body parts
- smart implants: biocompatible implants that can sense and actuate in order to repair or enhance a body function
SPORT WELLNESS
- Body control
- High tech gear
- Smart fields
- Positioning & posture
- Future training
- Fight obesitas
EU 7th Framework 2007-213

Health is second largest cooperative research theme in the EU 7th FW (after ICT)

1. Information and Communication Technologies 12670 million €
2. **Health** 8317
3. Transport (including Aeronautics) 5940
4. Nanotech, Materials and new Production Technologies 4832
5. Security and Space 3960
6. Energy 2931
7. Environment (including Climate Change) 2535
8. Food, Agriculture and Biotechnology 2455
9. Socio-economic Sciences and the Humanities 792

Main overall issues in FW 7 are:
- translational research (translation of basic discoveries in clinical applications)
  - data integration, systems biology
  - research on the brain and related diseases (alzheimer), aging, dna-genomics
  - infectious diseases: microbial, hiv/aids, malaria, tbc, sars, pathogenic
  - major diseases: cancer, cardiovascular, diabetes/obesity; other chronic diseases (e.g. osteoarthritis)
- the development and validation of new therapies and diagnostic tools
  - high throughput research
  - detection, prevention and monitoring: non-invasive or minimal invasive
  - new biomarkers, models/simulation, pharmacogenomics, targeting approaches, testing
  - innovative therapeutic approaches
  - innovative medicines (European Technology Platforms)
- optimizing delivery of health care to European citizens
  - two strategic issues: child health and the health of the ageing population
  - quality, efficiency and solidarity of health systems
  - enhanced disease prevention and better use of medicines
  - appropriate use of new health therapies and technologies
- methods for health promotion and prevention
sensors & smart implants
sensing & drug delivery
adaptive body correction

non invasive surgery
and minimal invasive surgery or treatment

healthcare IT
telemonitoring, right information right time

early diagnosis
molecular imaging
nanosensors, lab-on-chip

nanomedicine
nanoparticles for imaging & drug delivery

system biology
human modeling
physiology, biomechanics, biochemistry
Emerging health technologies: convergence of nano and biotechnology

Technology in life science is rapidly emerging. Thanks to the convergence of nanotechnology, biotechnology, ICT and cognitive sciences, many new technologies are in progress with a high potential impact on future health and health care system. A short list of the technologies of the future:

- Early diagnosis
- Healthcare IT
- Nanomedicine
- Smart implants
- Non invasive surgery
- System biology, chinese medicine

Convergence is also happening in areas such as:
- scientific instruments (nanosensors for biomarkers)
- analytical methodologies (quantum dot fluorescence, dna/proteomic arrays)
- new material systems (biomimic materials, self assembling materials)
- new pharma systems (nanomedicine, nanoparticle labeled drugs, theranostics)

Improving human performance and wellbeing

NBIC convergence can give us the means to deal successfully with the challenges to enhance human mental, physical, and social abilities. Better understanding of the human body and development of tools for direct human-machine interaction have opened completely new opportunities. Long term implications of converging technologies are in the key areas of human activity:

- societal productivity
- security from natural and human-generated disasters
- individual and group performance and communication
- life-long learning, graceful aging and a healthy life
- coherent technological developments and their integration with human activities
- human evolution, including individual and cultural evolution

Future scenarios of what converging technologies can bring cover many aspects such as:

- fast, broadband interfaces that enable human brain and machine interaction
- comfortable, wearable sensors for health monitoring and potential hazards
- robots and software agents with human like behavior and interaction
- more durable, healthier, more energetic body, and easier to repair
- adaptive machines and structures
- compensation for mental and physical disabilities
- superior intelligence-gathering systems, information anywhere
- intelligent environments leading to high efficient production and services
- vastly improved awareness of cognitive, social and biological human forces

(Converging technologies for Improving Human Performance, NSF/DOC-sponsored report, June 2002)
TNO S&I technology base

**Design & Manufacturing** (Jan Smits)
- rapid manufacturing of human related products (wearables, implants)
- scanning and measurement systems for customfit products
- monitoring, analysis and advisory systems for (human) motion and sport
- biomechanical modeling
- ambition: 100% focus on human systems

**Materials Technology** (Dick Koster)
- nanomaterials for bio-applications e.g. bioswitch, drug encapsulation, nanocarriers for pharma
- ambition: bioactive materials

**Industrial Modeling & Control** (Henri Werij)
- microfluidics, lab-on-chip, for bio/health applications
- ambition: microfluidic systems, in near future also process-on-chip

**Testing & Certification** (Odile Steijger)
- testing of (protective) clothing and devices for personal care, on functionality and comfort
- ambition: testing of personal care devices (teeth, hair, skin etc)

**Automotive** (Leo Kusters)
- biomechanical modeling (sport) based on Madymo
- links: human centric sensors in cars, human comfort in cars
- ambition: biomechanical modeling for rehabilitation (health), protective suits (defence)

**Microsystems** (Hans Sirks)
- assembly by wire, micro-assembling by human via telemachining
- antenna’s, senstenna as wearable/implantable sensor for human diagnostics
- ambition: telemachining for human, spin-off to medical (telesurgery)

**Opto Mechanical Instrumentation** (Wart Mandersloot)
- micro precision surgery, plasma cleaning for medical applications
- links: optics for the eye
- ambition: molecular imaging, biomolecular optical detection on chip, biosensors via nano-imprint

**Imaging Systems** (Hugo Vos)
- high intensity focused ultrasound for non-invasive surgery
- biometric detection op basis van vision
- robotics for hospital and revalidation
- dataretrieval & handling
- ambition: instrumentation and advisory measurement systems for medical & care
Technology selection

The required technologies for the three selected market functions body repair, drug delivery and assitive environment have been ranked against the following criteria: IP position, technical feasibility, development costs, time to market, market size, core business TNO, competition, generic applicability and ease of validation. High ranked technologies are:
- nanomaterials/bioswitch and nano additives
- focused ultrasound
- biomechanical (human) modeling
- sensor tags, senstenna

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<th>Healthcare selection table</th>
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<td>basic function</td>
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<td><strong>Drug delivery</strong></td>
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<td><strong>Assistive environment</strong></td>
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<td><strong>Body repair</strong></td>
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### TNO profile in Health

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<tr>
<th><strong>Category</strong></th>
<th><strong>Focus Areas</strong></th>
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<td>effectivity care system, evaluation technology/devices, security medical ict</td>
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<td><strong>Physical activity and health</strong></td>
<td>children, life-style determinants, heridatable, perinatology</td>
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<td><strong>Biomedical research</strong></td>
<td>diabetes, cardiovasculair, inflammatory/autoimmune, tissue repair</td>
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<td><strong>ICT in healthcare</strong></td>
<td>wireline, user centric innovations</td>
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<td><strong>Pharma</strong></td>
<td>screening, clinical studies, cell based in-vitro, animal, human translational</td>
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<td><strong>Toxicology</strong></td>
<td>necropsy, histological processing, histopathological evaluation</td>
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<td><strong>Microbiology</strong></td>
<td>microbial genomics, DNA, RNA and metabolites</td>
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<td><strong>Biomedicine, systems biology</strong></td>
<td>metabolics, transcriptomics, prognostic biomakers, chinese medicine</td>
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<td><strong>Nanomedicine</strong></td>
<td>nanoparticle encapsulation, (ultrasound) release on demand, lab-on-chip</td>
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<td><strong>Medical devices</strong></td>
<td>customized body repair, minimal invasive surgery, micro X-ray</td>
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<td><strong>Homecare &amp; Sport</strong></td>
<td>assistive environment, telemonitoring, biomechanical modeling</td>
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Surgery room of the near future: assistive environment & telepresence

autonomous, pro-active information and consultancy system

ASSISTIVE ENVIRONMENT

Telepresence
THE Surgeon
THE Anaesthesist
THE Radiologist
THE Internist

Cochrane database
EPD
Colleague

Information Mediation

vision, image, position, speech, sound

bloodpressure, O₂-saturation, cardiac output

ASSISTIVE ENVIRONMENT

photo’s, scans
protocols, lab reports
decursions, surgery reports
literature, internet data,
images, video, sound

acoustic arrays for
directional speech recognition

automated recognition of
scene, movements and gestures
Healthcare ICT

• Patient logistics (MEDCON)
  • patient tracking & planning, tracking & tracing consumables (RFID)
  • optimization clinical & care paths, GDMS concepts

• Knowledge management (IZIT cluster)
  • document and information retrieval, security
  • adaptive interfaces for EDP, adaptive multimodal interfaces
  • experimental EPD platform as testbed for new technologies

• Broadband applications (Teleokto, Okto, Freeband PNP / NBL)
  • integrate information, expertise and specialisms
  • separate use for diagnosis, consultation, information and treatment
  • business models, investments models

• Smart health (Freeband B@Home, FRUX, UAS, TUMCAT testbed / VitaValley)
  • ambient serviceplatform at home, monitoring and diagnostic systems
  • testbed services and systems
  • demand and user characteristics, personalized interfaces

• Telecare (ID-lab / VitaValley, IZIT, EZ, KPN)
  • body area network, condition and health monitoring (system level)
  • development new services for telemonitoring, diagnosis, treatment, rehabilitation
  • fieldlab’s
Sample preparation on chip for DNA extraction

Sample preparation on chip for fully automated extraction of early diagnostic biomarkers (DNA, proteomics, metabolites from (bio)fluids) and subsequent detection on biochips.

One reaction chamber system
• external fluid controls
• ultrasound for lysing & mixing
• magnetic bead extraction
Systems biology: from diagnostic markers to prognostic markers

The goal is to eliminate diagnostic markers and to use prognostic markers. Prognostic markers indicate the early development of a disease and therefore enable early treatment. This can be done with systems biology tools, looking at early changes in the metabolism. It requires sophisticated analytical tools and heavy statistics to detect changes in the wide variety of metabolic markers.

Prognostic biomarkers via metabolic & lipide fingerprinting, examples:
- meningitis
- cholesterol
- osteoporosis
- diabetes
Targeted drug delivery (release on demand)

**Nanomedicine:** nano encapsulation of drugs, release via bioswitch or ultrasound

**Focused ultrasound:** non invasive surgery and local drug delivery

- MRI brain
- US energy distribution
- Phased array ultrasound
Body monitoring & sensors
Non invasive treatment

high intensity focussed ultrasound (HIFU)
- thermal surgery, tumors and vascular (esp. brain tissue)
- localized drug delivery

therapeutic ultrasound
- tissue activation, wound healing, skin therapy
- transdermal drug delivery

Non Invasive Brain Surgery with HIFU
High intensity focused ultrasound is new and promising technology for non invasive surgery. Especially of interest for brain surgery but also applicable for tissue treatment and repair at other locations. It uses a focused array of ultrasound to generate a localized (1-3 mm) energy spot resulting in either cell lysis (high energy, tumors), tissue activation or local drug delivery (low energy). It is a 100% non invasive technique under MRI thermal imaging for guidance.

Transdermal drug delivery assisted by ultrasound
Micro invasive surgery

MIS robot: waferstepper technology in future surgery

New generation “Da Vinci” robot
• force feedback
• haptic feedback
• UMC, AZM, TU/e, TNO (IOP PE)
• long term: MRI & CT compatible system for surgery under real time vision

Miniature invasive X-ray source
• brachytherapy
Regenerative medicine, tissue engineering

Skin, Bone, Cartilage

Osteo-Arthritis Organ Patches

Anti-Cancer Vaccines Diabetes

Alzheimer’s Parkinson’s Disease

Nerve regeneration for spinal & limb repair

2005

2015

2020

2025
Custom fit, 3D scanning

3D Body scanning

HAL 3
Robotic assistance for elderly or infirm people, or those with disabilities

Backpack
Contains a computer with a wireless network connection

Battery

Actuators
Electric motors provide powered-assisted movement to the limbs

Angular sensor
Detects the angle of the hip, knee and ankle joints

Bioelectric sensors
Sensors attached to the skin monitor nerve impulses from the brain to the muscles indicating that a movement like standing or walking is about to take place. The signal is relayed to the computer where it is analysed and used to launch the actuators even before the subject's wearer moves

Floor reaction force sensor
Detects the user's centre of gravity
Pathogen
Pathogen-specific Antibodies
Natural Biochemical Signaling Pathway
Calcium Ions
Bioluminescent Protein/Molecule
Biosensor
Light Emission

Cantilever Sensor; Thundat ORNL

μ Biodiagnostic System
Electrokinetic Microsystems
Microfluidic Lab Card

Fluid Pumping: Electrokinetic / Pressure-driven
Mixing: Static, Diffusion Limited
Preconcentration: Stacking, IEF, ITP, PCR etc.
Separation: CE, LC etc.

Microdispenser: Fluid Metering
Multiplexing

Biosensors:
Optical: SPR, Fluorescence etc.
Electrochemical: Amperometric, Potentiometric etc.

Motorola Biosciences’ eSensor™ DNA Biochip
Nanogen’s NanoChip™ Microelectronic Array Cartridge

www.motorola.com/lifesciences/

Caliper Technologies’ LabChip™
**Bio sensors**

Thanks to miniaturisation down to micron & nano level:

- **small dimensions**
  - (mm, um, nm)
  - function integration possible (dsp, rf-wireless)
  - efficient thermal and material transport
  - cheap, easy for mass production
  - portable, point of analysis
  - disposable

- **small sample volume**
  - (uL, nL, pL)
  - fast response
  - high throughput
  - multi parallel analysis, matrix array
  - single cell/molecule detection
  - less chemical waste

- **high sensor-sample ratio**
  - high sensitivity
  - high signal to noise
Nanomedicine

The ageing population, the high expectations for better quality of life and the changing lifestyle of the society lead to the need for improved, more efficient, and affordable healthcare. Nanomedicine is defined as the application of nanotechnology in medicine. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale. Nanomedicine has the potential impact on the prevention, early and reliable diagnosis and treatment of diseases.

In nanomedicine, three areas are of special interest:

**Nano-diagnostics**, including medical imaging, for identification and diagnosis at earliest stage possible
- high sensitive, preferentially single molecule, detection of (early) biomarkers
- high resolution microscopic and spectroscopic techniques, both in-vitro as well as in-vivo
- high resolution in-vivo imaging techniques such as MRI, CT, PET and Ultrasound
- target specific contrast nanostructures for imaging
- theranostics: combination of diagnostic (targeted contrast agents) with therapeutic molecules (e.g. radio isotopes)

**Targeted drug delivery** and controlled release
- drug delivery microchip technology, implantable (e.g. automated glucose delivery)
- nanoparticles that can release on demand pharmaceuticals, triggered by bioreaction or by external forces
- dna loaded nanoparticles that can be transfected into cells to repair malfunctioning of cells

**Regenerative medicine**, tissue engineering
- in-situ tissue regeneration and repair with bioactive (DNA carrying) particles that induce specific cell growth
- biomimic nanostructures to be used in scaffolds for optimal tissue uptake and regeneration

Single molecule detection (DNA, proteomics) by Jeff Wang, Johns Hopkins Univ, USA
Nanowire molecular sensor concept, NASA Ames:
- electrochemical detection by electrical current
- weight: change in mechanical resonance indicates molecular weight

DNA array: DNA probes on nanotubes
- electrochemical detection
- and/or fluorescence

Electronic nose on chip, ppb/ppt gas/vapor detection
- change in mechanical resonance by molecule absorption
- detection via laser readout
Nanosensors

Nanotechnology has great potential for sensing devices since the nanoscale enables a high surface area coupled to a very low mass, featuring a high sensitivity and a high signal to noise ratio at a level that can not be obtained on the macro scale. Also the high functional density and the ability to produce matrix-array sensors have many advantages.

The following sensing techniques at the nanoscale are being employed:
- mechanical resonators such as nano-cantilevers: the shift in resonance is a measure for the absorbed particle/molecule
- optical resonators (optical cavity): resonance shift upon presence of change in optical index due to molecular absorption
- electrical/electrochemical: measuring charge transfer in contact with a nanowire, can be promoted with enzyme or catalyst
- electrical resistance: conductivity over a nano-porous (nanoparticles, nanofibers) substrate
- magnetic detection (GMR) via magnetic nanolabelling of molecules
- specific, targeted detection via DNA functionalized nanoparticles, with subsequent electrical or optical read-out
- single molecule detectors, enabled via quantumdot fluorescent labeling
- lab-on-chip systems for processing, upconversion and detection of DNA and proteomics

Chemiresistor with cnt’s or nanofiber fabric, for gases (NASA Ames)

MOx gradient matrix gas sensor, ppb level, ForschungsZentrum Karlsruhe
Implantable sensors

Optical dome

Lens holder

Illuminating LEDs

Lens

Battery

Antenna

Camera in a pill by Given Imaging (Israel), PillCam ESO. Over 150,000 patients since 2001

Optical sensors

SERS: Surface enhanced Raman scattering

SERS on fiber tip for tissue analysis
FMCW radar (2.4, 9, 8, 76, 6 GHz)

- Portable
  - detects motion, distance, direction
  - low power, handheld, low cost
  - antenna array
- Non contact measurement
  - heartbeat (through clothes)
  - respiration rate (through wall)
  - skin cancer detection
- In body imaging
  - breast cancer imaging
    (1-2 mm)

heartbeat and breathing

breast cancer

combined video and radar

through clothes vision

baby surveillance
Diagnosis with vision systems

Tongue analysis by vision (Taiwan, USA)

Wound imaging

Retina scan, detection of macular edema (diabetes) with OCT
Evaluation quality of healthcare

QMT
To support hospitals improve their quality TNO developed the ‘Quality to Medical Technology’ quality system. This system creates a control circle that ensures a shorter response time to errors and lower costs. A smoothly running QMT can save 6 to 10% on the costs of medical technology management. The Medical Centre for Rijnmond South was awarded the first QMT certificate in 2002.

QMIC
The TNO QMIC certificate for website stands for approval of content, information and transactions that are being serviced by the website/
Future sport training

Future sporters and trainers will make use wireless technology to get access to real time performance data, physical and mental condition. Together with expertise from human modelling for interpretation, an intelligent analysis and decision making system is obtained to for immediate responsive actions or future training scheduling. The necessary tools require the following technologies:

- wireless, real-time body sensors for heart rate, position, motion, acceleration, energy/fatigue
- 3D-visualisation and analysis of posture, movement, performance
- biomechanical modeling for analysis muscle and skeleton loading
- physiological modeling for energy and heat balance (food and clothes)
- optimisation of training schemes
- design of sport equipment, clothes and food
- optimisation of sporting accommodations
TNO zorginnovatie programma 2007 2010
systeeminnovatie

- **Patient empowerment**
  Patient veiligheid, patient empowerment:
  informatie, kennisoverdacht, gedragsbeinvloeding

- **Ketenzorg**
  Informatie: ICT info & infra structuur, networkdevices & services,
  ICT systeemontwikkeling, uitwisselbaarheid, koppelbaarheid
  Organisatie: Arbocuratief, Slimmer werken in de zorg, Telemedicine,
  nieuwe zorgsystemen, kennismanagement, decision tools

- **Medische technologie**
  Technologie voor thuiszorg, transmuraal, eerste lijn
  assistive environment & selfcare, targeted drug delivery, medical devices & implants

- **Virtuele proeftuin, fieldlab**
  Virtuele testomgeving nieuwe zorgsystemen

- **Transitiemanagement**
  Implementatie en pilot trajecten

**Participatie van de hele keten:**
patienten & artsen verenigingen
zorginstellingen, zorgverzekeraars
overheid,
bedrijven (ICT, medical equipment)