TNO report

Research program 2019
Topsector Life Sciences & Health

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Program 2019
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1.1 Summary

The goal of TNO's Biomedical Health research program is to help individuals, professionals and industry to efficiently develop (personalized) treatments to maintain health, well-being, vitality and to prevent or cure diseases, with main focus on metabolic and immune health. This goal supports the mission of Topsector Life Sciences & Health ('LSH') **-vitally functioning citizens in a healthy economy-** and will also effectively contribute to solving one of the main societal challenges **-Health & Care-** identified by Dutch Ministry of Health, Wellbeing and Sports ('VWS').
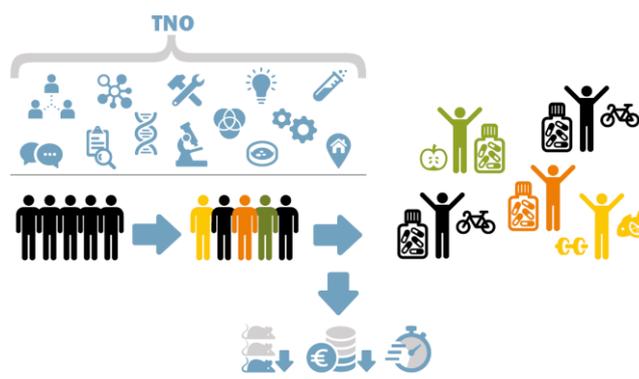
By 2022 we want to have achieved the following:
Enable lower attrition rates and more efficient drug and other intervention development:
- Demonstrate with partners that current pre-clinical trajectories can be improved (reducing costs, time and animal use) when new advanced translational models are employed.
- Demonstrate that smaller clinical trials for a novel therapy can be achieved by targeting the right patient population.

Help improve metabolic and immune health:
- Demonstrate metabolic and immune health improvement by (combination of) food, lifestyle or medication therapy in stratified groups of patients; right drug and intervention for the right patient.
- Prove that tailored interventions contribute to vitality of the citizens as well as the quality of health care and cost management.

To progress towards these above goals, in 2019 we will:
- Demonstrate together with industrial partners that efficacy of drugs in humans can be predicted by using in-silico, in-vitro and ex-vivo human approaches, without testing in animals.
- Together with partners develop advanced microtracer techniques that will help to bring novel cancer treatment faster to the patients, enabling better cure.

- Develop a stratification method based on microbiome, applicable in development of personalized lifestyle interventions in prevention and also in cure in for development of new drugs.
- Start the development of an immune flexibility test, based on dynamic biomarkers and host-microbe interactions, which will help companies to measure the effect of their immune health interventions in prevention and cure of chronic inflammation.
- Develop V1.0 of a tool for diagnosis in which different aspects of health and vitality are integrated (metabolic health, mental health, socio-economic environment, activity); the tool will help define personalized approaches in prevention, cure and care.

1.2 Description

1.2.1 VP Biomedical Health

The global healthcare industry grapples with an unsustainable cost trajectory. Most economies face increased demand for healthcare services by an expanding pool of consumer/patients and by growth in costly chronic disease management. Furthermore, high attrition rates in drug development contribute to expensive medication and to higher health care costs. Innovations in several areas may offer solid solutions for improving the drug development process, for increasing the quality of care and population health while containing costs.

Our program is founded with the firm believe that through development and application of advanced tools and technologies and knowledge on models and mechanisms of disease (onset) in metabolic and immune health, we can enable more efficient development of personalized treatments for prevention of these diseases, delay or cure the onset of diseases and thus reduce healthcare costs. In personalized treatments, we recognize that every individual is unique, not only with respect to their physiological and genetic background, but also related to their mental status and social context.

1.2.2 Goals for 2022

The overall goal of this program is to help individuals, professionals and industry to efficiently develop (personalized) treatments to maintain health and wellbeing and to prevent or cure diseases with main focus on metabolic and immune health.

The knowledge we develop together with partners will enable earlier detection of metabolic and immune diseases, help their prevention and also improve the efficacy of their (drug) treatment. The novel tools and technologies developed by TNO and partners will also contribute to efficient drug development, lower the attrition rates and help to achieve a more efficient clinical study design and thus help to bring the right drugs to the right patient faster.

More specifically we will:
Enable lower attrition rates and more efficient drug and other intervention development by:
- Development of translational and better predictive models (in-vitro, ex-vivo, in-vivo, in-silico), by development of advanced measurement methods, and by increasing the information density of early clinical trials.

- Development of advanced in-silico tools for risk and safety assessment of targets and treatments as well as assessment of biomarker efficacy.

Help improve metabolic and immune health by:
- Better understanding of disease mechanisms, thus enabling the development of better predictive models.
- Identification and validation of (novel) translational biomarkers for early detection of metabolic and immune disease complications.
- (co-)Development and (co-)implementation of tailored intervention strategies for improvement of metabolic and immune health.

Tools and models for efficient drug and other intervention development
Within this research line we will **address the need for better predictive, translational models and tools for efficient drug and other intervention development**. We will focus on development of validated, highly predictive translational models (in-vitro, ex-vivo, in-vivo and in-silico) that assess the efficacy, kinetics and toxicity of various interventions (drugs, foods, lifestyle) in humans, applicable in the entire product development trajectory. We will contribute to innovations towards animal free testing (e.g. 'organs-on-a-chip', candidate selection directly in humans using microdosing and AMS). We develop tools and models that predict biological outcomes of the modulation of a biological process or protein target in-silico (risk assessment) and better mimic (personalized aspects of) physiological and disease processes in humans. The development of the tools and models is based on better understanding of the mechanisms of onset of inflammation, metabolic and immune health dys-regulation (including complications). Data mining tools and systems biology approaches will be developed for **identification and risk assessment of targets and identification and efficacy assessments of treatments and biomarkers**.

Improvement of metabolic and immune health through personalized interventions
Within this research line we will focus on **identification of (dynamic) biomarkers for early detection of metabolic& immune disease and corresponding health complications, identifications of new targets for treatment of metabolic and immune disease**. Systems biology methods will be used to identify biomarkers based on genes, proteins, metabolites, specific microbiome compositions or specific lifestyle aspects. The biomarkers can be used for **stratification of patients in clinical trials** and for development and implementation of personalized intervention strategies. A logical follow-on application for patient profiles and biomarkers is the ability to provide health care professionals with concrete advices on what preventive measures or therapeutic interventions fit best with the biological profile of their patient. Preferably these advices will be laid down in standards of care for the various diseases.

We will develop **personalized interventions for maintenance and improvement of metabolic & immune health and well-being. We will help to implement personalized and stratified interventions in specific target groups**, children (immune and metabolic health and pediatric microdosing), adults (immune and metabolic health) and (pre)obese persons, (immune and metabolic health) and elderly (metabolic decline of skeletal muscle with age), but also cancer patients which might benefit from metabolic and immune health improvement. This line is closely connected to TNO's research program Digital Health Technologies.

1.3 Program 2019

In 2019, we will continue to expand our activities in public-private partnerships and shared research program(s) in which we will develop the technologies and knowledge necessary to achieve the set goals program goals. The PPP projects contribute to the LSH focus areas **prevention, cure and care**.

In figure 1 several examples of existing and planned collaborations that are planned to start in 2019 are shown, as well as their contribution to the program goals. In the course of 2019, new ideas/ technology needs will be identified that will be used for the setup of new collaborations. The activities within these PPP's will lead to achievement of several knowledge and technology deliverables. Each deliverable contributes to one or more program goals. The table also indicates the LSH roadmaps to which the newly developed knowledge and technology will contribute.

selection of (planned) collaborations	2017	2018	2018	2019	2019	2020	2020	2021	2021	2022	2022	contribution to program BMH goals	main deliverable	Roadmap LSH
Tools, models for efficient drug development														
SRP food allergy and immune health												2,5	immune health risk assesment tools	7
PPP Ex-Vivo models as an alternative for animal testing												1,3	better translational models	5
PPP Animal free drug development												1,3	better translational models	5
PPP in silico target discovery tools												1	automated drug target evaluation tool	5
PPP microtracers in Antibody drug conjugates for cancer												1	advanced analytical tools	5
PPP Anti-Clostridium												1,4	tools for intervention development	7, 6
Metabolic and immune health improvement														
PPP NASH Biomarkers												3	metabolic health biomarkers, NASH	1
PPP Phenflex 2, phenotypic flexibility in prevention												3,5	novel biomarkers metabolic health	3,8
PPP Microbes and immune health												3,5	biomarkers and targets immune health	7
PPP Muscle health and gender differences												1,3,5	mechanisms and translational models	7
PPP Netherlands Institute for Lifestyle as medicine												4,5	tailored interventions metabolic health	7,8
PPP enhancement of medical treatments by improved metabolic health												1,3,5	tailored interventions metabolic health	7
PPP Pro Liver, targets for NASH treatment												1,3,4	insight in mechanisms metabolic health	1,5
SRP Global, Organ cross talk in metabolic health improvement												1,3,4	mechanisms and translational models	1,8

Legend:
- 🟥 PPP just signed and started
- 🟦 (light blue) PPP in preparation
- 🟦 (dark blue) PPP already in execution
- 🟩 PPP extension/ expansion in preparation

Figure 1: **Selection of current and planned PPP collaborations and their contribution to the Biomedical Health research program goals and the roadmaps of Topsector LSH**. BMH program goals: (1) Development of translational and better predictive models and measurement methods, (2) Development of advanced in-silico tools for drug discovery, (3) Better understanding of disease mechanisms, (4) Identification and validation of (novel) translational biomarkers, (5) (co-)Development and (co-)implementation of tailored intervention strategies for improvement of metabolic and immune health. LSH roadmaps: (1) Molecular Diagnostics, (3) Homecare and self management, (5) Pharmacotherapy, (6) One Health, (7) Specialised Nutrition, health and disease, (8) Health technology, assessment, individual functioning and quality of life.

Program line tools and models for efficient drug and other intervention development

- Device to scale up the number of samples measured with AMS for support of microdosing studies (goal 2).
- Improved in-vivo and in-vitro translational models for NASH/fibrosis (goals 1 & 3)
- Demo case of effects of dietary interventions in early life on brain development in in-vivo models (goals 1 and 3).
- (Semi-) automated in-silico platform for drug and biomarker discovery (goal 2).
- Proof of concept of ex-vivo perfused pig liver model as an alternative to animal experiments for application in pharmaceutical industry (goals 1 and 3).
- 3D liver-function (NASH/Fibrosis) model on a chip, proof of concept (goals 1 & 3)
- Human intestine model on a chip, collaboration with early research program Organ-function-on-a-Chip (goals 1 and 3).
- List of potential circulating biomarkers for early detection of liver fibrosis in patients (goals 3 and 4).
- Protocol for application of microdosing techniques for studies on Antibody drug conjugates to identify (toxic) metabolites (goal 1).
- Platform for functional microbiome analysis (goals 1 and 3).

Program line Improvement of metabolic and immune health

- Protocol for metabolic health improvement interventions as a support to increase the efficacy of standard drug treatments for e.g. gut cancer (goals 4 and 5, in collaboration with early research program Personalised Nutrition).
- First demonstrator assessment of immune health risks based on food consumption and food composition databases (goal 2).
- Next version, V2.0 of the Healthspace diagnostic tool which integrates multimodal data (from different domains) in addition to plasma biomarkers (goals 4 and 5).
- Shared research program with industrial partners for development of interventions targeting multiple organs in improvement of metabolic health, cross talk cross-talk between liver, adipose tissue and gut (goal 3 and 4).
- First description of stratification of morbidly obese subjects based on individual organ health (adipose, liver, gut) enabling stratified interventions (goals 3 and 4).
- Automated tool to generate personalized health reports (goal 5, in collaboration with VP Digital Health Technologies).

Internal collaboration:

In order to achieve the set goals we will develop new interventions, knowledge, tools and technology in two program lines which are shown in figure 2.
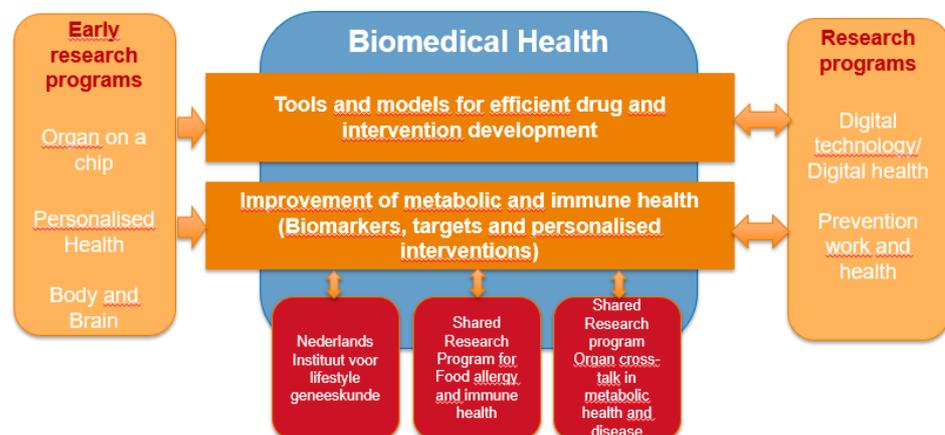

Figure 2: Program lines of research program Biomedical Health. Connection to three early research programs (Organ on a Chip, Personalised Health, Body and Brain) and strong collaboration with research

program Digital Health Technologies, and Prevention, Work and Health. In 2019 Biomedical Health is supporting 3 shared research programs (the National Institute for Lifestyle as Medicine, SRP Food Allergy and Immune Health, and SRP Global on organ cross-talk (in development))

This program will only be successful if we succeed in realizing further (project based) collaboration with the experts from other Units within TNO, specifically from:

- **Unit High Tech, Space & Chemicals**: Optics, Holst Center, Nano-instrumentation, Materials and Solutions for Organs on chips technologies for **development of novel materials that will be used in better translational in-vitro and ex-vivo models**. In collaboration with these departments, also new readouts for use in combination with in-vivo translational models are explored.
- **Unit Defense, Safety & Security**: Distributed Sensor Systems, Human Behavior and Organizational, Innovations Training & Performance Innovations, Modeling, Simulation& Gaming, for knowledge and approaches in **personalized interventions**.

In many cases collaboration has already been realized, through collaborative projects and early research program 'Personalized Health', early research program 'Organ-function-on-a-Chip', and Seed early research program 'Body and Brain'.

External collaborations and connections.
This program is directly connected to the mission, ambition and objectives of **topsector LSH (Knowledge and Innovation Agenda 2018-2021** (see section 1.3). The results of this program will directly contribute to the tackling of the societal challenge: **vital citizen in a well-functioning economy**.

Our PPP projects will continue their contribution to the roadmaps of topsector LSH:
1. Molecular Diagnostics
3. Homecare and self management
5. Pharmacotherapy
6. One Health
7. Specialised Nutrition, Health and Disease
8. Health technology assessment, individual functioning and Quality of Life

The program is linked to the following NWA routes:
- NWA route Personalised Medicine
- NWA Gezondheidszorgonderzoek, preventie en behandeling
- NWA route Kwaliteit van de omgeving
- NWA route Regenerative medicine

Examples of operational strategic PPP's that are supported by LSH include:
- **Personalised Nutrition & Health**: the ultimate goal of the consortium is to enhance the health and wellbeing of society by empowering consumers to choose and maintain an optimal personalized diet & lifestyle.
- **Metabolic Health Innovations from care to cure**: this PPP aims at reversing or curing lifestyle related diseases by changing lifestyle. The initial focus is on type 2 diabetes with the aim to cure this disease within 10 years. This PPP is the first step towards a joint research and implementation program, the Joint Innovation Centre between, amongst others TNO, LUMC and a number of industrial partners.

With the technology and knowledge (to be) developed with will effectively contribute to the innovation in one of the big societal challenges identified by the **Ministry of Health, Wellbeing and Sports, Heath and Care**, as described in the 'Kamerbrief' Mission Driven Innovation Policy with Impact, July 13th, 2018.

This program also has a number of strategic collaborations with academia, such as University Medical Center Utrecht in the area of immune and metabolic health, Wageningen University and LUMC in the area of metabolic health and physiology, ACTA metabolic and dental health, University of Nijmegen for links between metabolic health and healthy brain development as well as pediatric research. We are setting up a collaboration with University of Maastricht in the area of liver health and advanced molecular readouts, VUMC for microtracers and PET imaging. In addition to academia we also have strategic collaboration with several companies that are often partners in PPP projects, such as BioFortis, PRA, CHDR (Human studies) and Nordic Biosciences (biomarker measurements).

We will be developing new international EU-project consortia for calls that will be published late 2018 and in 2019 with focus on metabolic health and translational in-vitro models. We are participating in several consortia applying for grants within the NWA call in 2018 and 2019.

Apart from being linked to the Knowledge Agendas of topsector LSH, this program also links to hDMT (a strategic PPS, national initiative in the area of organ-on-chip technologies, TNO became partner in 2016), has good connections with policy makers at ZonMW. We align with **One Health, Humane Meettechnieken** (3/4V) **and Animal free innovations** and are currently strengthening our links to the **European Medicine Agency (EMA)**.

1.4 Dynamics

The recent decision-making on the Dutch Food Institute has important implications for the collaborations and expertise in the roadmap Food & Nutrition. The program High Quality Products left to DFI, Food Safety (Food allergy) and Healthy Food became part Biomedical health as of 2018 and jointly define the current focus on metabolic and immune health. TNO will continue research on health-related nutrition issues.

E-health, digital health and medical devices (collaboration with the Van 't Hoff program) have shifted from the roadmap Biomedical Health to Digital Health Technologies in 2018. The collaboration between Biomedical Health and Digital Health Technologies is very strong and the programming of the two research areas is coordinated.

Considering the even stronger focus on health aspects of nutrition as from 2018 and also a strong pharma background of Biomedical Health Program, our ambition is to develop more PPP projects in which Pharma and Nutrition companies work on common goals.

We will align our technology development also with the needs of pharma industry by connecting to EMA, which will move to the Netherlands in the near future. First discussions with EMA took place in Q2 2018 and will continue in Q4 2018.

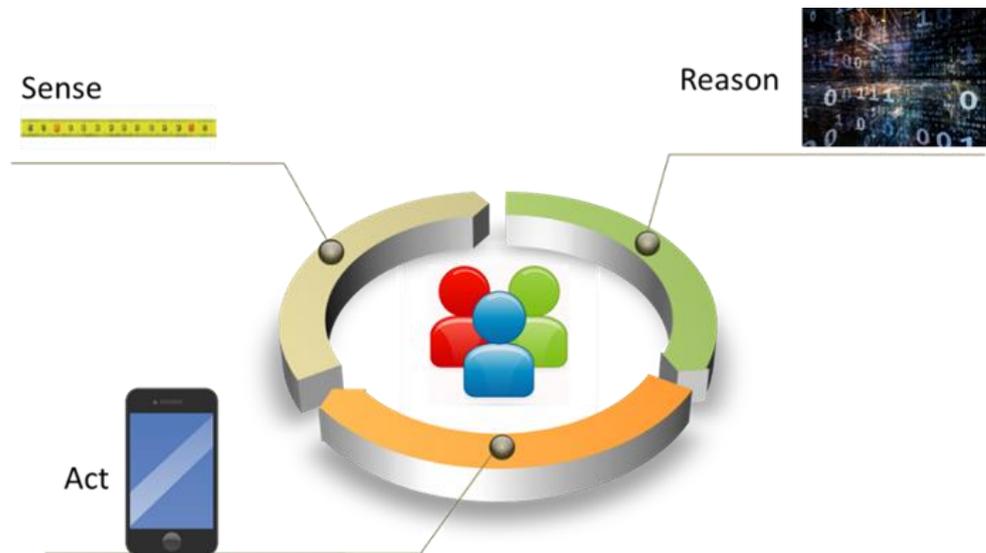# 2 VP Digital Health Technologies

Program 2019
Contact person TNO: Jildau Bouwman
Contact person LSH: Nico van Meeteren

2.1 Summary

The world around is digitalizing, this also holds true for health care. People gather masses of health data using apps that record their pulse rate, daily activity, diet, etc. It is not only members of the public who are interested in this data, it is also valuable to scientists. Such Real World Evidence data together with standardized health data have the ability to create new models and improve existing models and software applications that provide health and medical advice. Based on these models personalized health advice tools can assist both patients and healthy individuals, by offering guidance about their health and lifestyle and prevent disease.

The research program Digital Health Technologies ("DHT"), together with partners outside TNO (including several SMEs), takes up this approach bringing together new medical knowledge, data and information technology services and solutions as well as knowledge about lifestyle change and behavior. As the whole system is directly connected to individuals by design, citizens can also specify their needs. Health and healthcare can benefit from the secure registration of personal data from birth to death, and from its subsequent use in providing personal support or advice, as well as in predictive models. The developed systems can be used by medtech companies and by data brokers that want to use health data in a system that is private-by-design.

The goal of this 2019 program is to contribute to the implementation and operation of innovative digital health interventions and bring together three focus area's –Healthy Youth, Sustainable Employability and Metabolic Health– to maintain health over one's personal life span. The program will develop knowledge, (ICT-) solutions,

facilities and services to apply in the focus area's in three program lines with the following deliverables for 2019:
1. **Sense**: further implementation of the FAIR principles and thereby connecting this data of the different domains.
2. **Reason**: distributed learning is implemented so that we can train our models on health data that are stored on smart phones without ever leaving the phone.
3. **Act**: digital resources (interfaces and apps) for giving feedback, monitoring and supporting behavioral change are implemented in the iJGZ platform.

2.2 Description

2.2.1 VP Digital Health Technologies

We face tremendous societal challenges in health care due to an aging population, an increased amount of chronic/lifestyle diseases and a rapidly rising shortage in staff[1]. One of the most important challenges in the coming years for health care in the Netherlands is to create and maintain an effective, high quality and financially sustainable healthcare. It is paramount to improve all three components (quality, access and costs) at the same time[2].

An important step towards this goal is to enable and support people in making healthy choices and pursuing a healthy lifestyle. This requires first of all in-depth knowledge of biomedical and behavioral aspects of (improving) health. With this knowledge validated and reliable predictive models for health and disease can be developed, as well as personalized interventions to improve health and maintain a healthy lifestyle, at home and at work. Next, these interventions have to be delivered to people by providing personalized advice, monitoring effects and effectiveness of the changes in a person's life and lifestyle and giving feedback to support sustainable behavioral change (personalized health).

To enable the aforementioned steps we need to integrate health technologies and data science technologies with in-depth knowledge of biomedical and behavioral aspects. This raises numerous issues, from dealing with big data to secure privacy and data, from seamless monitoring to interaction design for small smartphone screens, from legal issues to viable business models for all value adding parties and much more. It requires a truly integrated and multidisciplinary approach to solve these issues and deliver effective digital tools for a healthy life and related research.

The research program Digital Health Technologies, together with partners inside and outside TNO, takes up this approach bringing together new medical knowledge, data and information technology services and solutions and knowledge about exposure, lifestyle change and behavior. New insights from youth healthcare, the sustainable employability of employees, exposure science, biomedical research are combined with health technology and big data technologies, so that data from cradle to crave come together. This program is directly connected to the mission, ambition and objectives of the **topsector Life Sciences & Health (Knowledge and Innovation**

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[1] Topsector HTSM Healthcare 2015 Roadmap , Editors: Casper Gares (Philips), Peter de With (Eindhoven University of Technology), Frans van der Helm (Delft University of Technology) and Nancy Westerlaken (TNO)
[2] Big Data Value Association: needs, opportunities and challenges TF7 Healthcare subgroup 12/21/2016

Agenda 2018-2021), is linked to the **Knowledge Agenda of the Societal Theme 'Work and Health'** and is linked to the following **NWA routes**:

- NWA Op weg naar een Veerkrachtige Samenleving
- NWA Waardecreatie door verantwoorde toegang tot en gebruik van big data
- NWA Jeugd in ontwikkeling
- NWA NeurolabNL

2.2.2   Goals for 2022

The goal of the program is to contribute to the implementation and operation of innovative digital health interventions in three focus area's -**Healthy Youth**, **Sustainable Employability** and **Metabolic Health**- by developing knowledge, (ICT) solutions, facilities and services and is structured in the following three program lines:

1. **Sense**: optimal and innovative ways of measuring, sensoring and data collection in the health and labor domain.
   Goal: seamless, (non-) invasive 3 measuring, monitoring and collecting data, compliant with privacy and security demands for knowledge application, validation and follow-up research.
2. **Reason**: transform knowledge and research outcomes into digital models, applications and advice and process the necessary big and personal data.
   Goal: transform data into knowledge and advice.
3. **Act**: digital resources (tools, methods) for giving feedback, supporting behavioral change and monitoring, focused on end user empowerment and shared decision making with a professional.
   Goal: empowerment of individuals by providing data-based feedback and advise.

The development of these innovations takes place in close collaboration with the experts in the focus area's in order to maximize the chance of successful implementation, and also recognizing the importance of knowledge about the conditions for operational and commercial success. In this respect this program is supporting and enabling TNO programs with regard to Healthy Youth, Sustainable Employability and Metabolic Health domains. Our aim is to be the digital knowledge and information provider for JGZ (youth health care services), sustainable employability and metabolic health.

2.3   Program 2019

2.3.1   WP1: Sense

Research and development in this program line is aimed at innovations for measuring, sensoring and data collection in the health and labour domain. Goal: seamless, (non-)invasive measuring, monitoring and collecting data, compliant with privacy, data ownership and security demands for knowledge application, validation and follow-up research.

Main research / innovation questions:

- How can digital biomarkers and real world evidence data improve health care?
- Which digital biomarkers serve as proxy for health outcomes or for health relevant processes?
- Which Real World Evidence data is relevant to improve health advice models?
- Which sensors are linked to these processes?
- Where can the relevant data be stored? How do we connect the data stores?
- How to implement privacy, data ownership, and security measures?

- How should we store health and health related data in terms of privacy, ownership and security?

Technology / knowledge required:
- Composite & digital biomarker development
- Sensors & sensing methods/ development
- Sensor/sensing search & selection
- Data platform
- Communication framework
- Ontologies
- Data safety solutions

Work in 2019:
- In 2019 some development will be done of the streamlining of our data over the three different domains. In an internal project we will harmonize the data of Biomed, child health and NEA by implementing the FAIR principles and using the framework that has been developed in 2018.
- With the DHT Hackathon 2019 we will build further on the network of biological data experts. Use cases that will be worked on will include questions like: 'How can personal nutrition be used in health care for faster recovery after hospitalization?' and 'What is the benefit for employers if they stimulate health advice for their employees?'.
- We will improve the data sharing and reuse of data in the food and nutrition community further by active participation in Food, Nutrition and Health-RI, JPI HDHL, HealthRI and ELIXIR. We will work towards project proposals for the Food cloud demonstrator call and the ESFRI roadmap.
- In 2018 a project proposal was send in on the Personal health train in the NWA call. In this project TNO will bring in its expertise on secure data sharing and preventive & personalized advice systems.
- An operational Health Data Cooperative (governance and facilities) where people can execute their property and management rights on their own personal and health data; the tool is actively used in a human study (diabetes challenge) in the PPS HDC.
- Measuring health in the real world is still hard. We lack tools to analyze the full range of aspects of health. From the systems biological knowledge obtained in VP BMH we will search for possibilities to measure health with non-invasive techniques. In 2019 we aim to automate this search over different digital resources.
- In the PPS project a beta-version of a Health Data Cooperative (governance and facilities) where people can execute their property and management rights on their own personal and health data will be implanted and used in a human study (diabetes challenge). In addition, the privacy dashboard will be developed in the related PPS.
- We will work towards PPS projects were we will develop Do-It-Yourself (DIY) measurements based on the needs from our commercial partners and in line with the goals in the roadmap (e.g. an oxidative stress sensor, a watch for allergy).

2.3.2   *WP2: Reason*
This WP aims at the processing of big (health) data and personal (health) data and to combine this with domain expert knowledge and in order to transform it into A.I. (advice) models. Goal: Combine knowledge and data and transform it into

diagnostics, interventions and knowledge leading to personalized advice and behavioral change.

Main research / innovation questions:
- What are the requirements/limitations/challenges for building a decision support systems based on explainable artificial intelligence?
- Can we build a (data driven, hybrid model) that quantifies health based on non-invasive acquired data?
- How can we improve our Bayesian nutritional advice models for disease?.
- How do we create A.I. models without a central data repository (responsible A.I.)?
- How can we optimally integrate publicly available data to get the best insight into the safety and efficacy of new drug targets?

Technology / knowledge required:
- Data processing (encrypted data; decentral analysis; safe exchange and storage)
- Integration of sensor data with advanced data-assimilation techniques
- Interoperability and standardization
- Statistical Analysis Tools
- Visualization
- Data interpretation: generic platforms for knowledge model/algorithms and biological interpretation
- Biological interpretation: finding meaning and causality: Hybrid models (together with ERP AI)
- Simulation models
- Contextualization
- Self-learning and predictive analytics
- Client/patient profiling. Data security/privacy: governance of health data

Work in 2019:
- For streamlining our work and improvement of our data analysis pipelines we will further implement SOPs (Standard Operation Procedure) and frameworks for sharing of script (an internal project).
- Innovative modeling techniques, including distributed learning and hybrid modeling, will be implemented in several (commercial) projects. This will be done in interaction with early research program Personalised Health and AI. These new modeling techniques will be also used to update the health space model that will be redeveloped based on the new data from the PPS Phenflex. Moreover, data will be combined from the different domains, to improve diagnostic and advice (e.g. what is the benefit for employers if they stimulate health advice for their employees).
- Models for health advice will be further developed, for instance the work done on a diabetes model in the FP7 project Power2DM, will be implemented in a project plan for a H2020 call.
- We will improve Do-It-Yourself (DIY) measurements by improving algorithms behind them in specific PPS projects.
- Prototype of either a drug discovery or biomarker identification model will be developed for TargetTri, security of TargetTri will be further developed and if possible a PPS will be initiated on one of these topics.

2.3.3   WP3: Act
This WP aims at digital resources (tools, methods) for giving feedback, supporting behavioral change and monitoring, focused on end-user empowerment and shared decision making with or without a professional. Goal: empowerment of individuals and healthcare professionals by providing data-based feedback and advise and the digital tools therefor.

Main research / innovation questions:
- How can we use ICT (feedback, monitoring, information supply etc.) to support personalized life style interventions?
- How can we create a digital twin that helps reaching particular health goals?
- How can we use digital tools to bring and keep people on board in life style advice systems (digital persuasion)?
- How do we keep people compliant with eHealth applications (predict risk of stopping; offer interventions to prevent people from stopping or stimulate restart)?

Technology / knowledge required:
- Behavior science (including persuasive technologies)
- E-learning (including applied gaming)
- Human-machine interaction
- Personalized design
- Applications for interactions

Work in 2019:
- Implementation of new methods for digital feedback in the interfaces for usage in three focus areas and add interaction design to our toolbox (in the project proposal for the Commit2data call).
- APIs in the different TNO projects and programs will be harmonized: linking PPS PNH, iJGZ Exposome. This will be done by implementation of the framework delivered in the DHT hackathon 2018.
- Development of apps that integrate TNO's knowledge on biology, physiology and sociology, so that we can deliver wellbeing advice, this will be done together with (commercial) partners in PPS projects.
- The privacy dashboard will be extended to a system privacy dashboard, so that the privacy of all tools and application in an advice system can be overseen at once.

2.4   Dynamics

The DHT program started in 2018, in which digital knowledge from the VP's Biomedical Health, Youth and Sustainable Employability were brought together. We have intensified the interactions between the programs and research groups on the digital agenda. For this a framework for sharing and harmonization of scripts was developed, which will be implemented in 2019. In 2018, the first DHT hackathon was held where data scientists from different groups have worked together closely to get to know each other's expertise, to work towards new ideas and to connect data from different sources. The hackathon will be programmed in 2019 again.

Developments in the program were based on the needs of the other VPs within TNO unit Healthy Living. Digital tools and solutions from the early research program Personalised Health landed in the PPS HDC. During the year interactions were

sought with the early research program AI. This interaction will be intensified during 2019.

The development of the iJGZ platform initiated in 2018. In the PPS PH (this program) and the Seed early research program ExpoSense (VP Sustainable Employability), technically, similar platforms will be developed. This program will actively align the work between this projects.