Innovation is only innovation
when it is implemented in daily practice

PHC Catalyst

Implementation barriers for PHC in the Netherlands

Others see the average, we see you!

The average patient is a myth. It's time to treat the individual.

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Personalised Healthcare Catalyst

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Foreword

Innovating is not innovating without implementing!

Since 2018, the Personalised Healthcare (PHC) Catalyst Alliance has been active to increase understanding of the importance, opportunities and challenges for personalised healthcare. For more information on the PHC Catalyst, please refer to the policy plan.
Currently, only a fraction of humanity receives truly personalized care. This has several causes. First, healthcare systems struggle to implement innovations in daily practice. Second, PHC is constantly evolving, so it is never 'finished'. But even innovations that can be implemented encounter barriers. The PHC Catalyst Alliance is committed to accelerating the transition to personalized care by creating a receptive environment that makes optimal use of all relevant available data, tools, knowledge, and applications in the field of PHC.

We use the following definition for personalized healthcare:

> "PHC is a person-centered health paradigm in which prevention, diagnosis, treatment and monitoring are based on relevant biological, environmental and behavioral characteristics of the individual."

How can we ensure that all innovation efforts and investments around PHC get the maximum return?

Both inside and outside of PHC, a great deal of importance is placed on answering this question. Research shows that the 'innovation paradox' is persistent, meaning that many promising innovations are ultimately never (fully) implemented. The success of an innovation is only 25% determined by the innovation itself, the other 75% is determined by social innovation: the system innovations and/or changes that are needed to implement innovation in daily practice.

Where in general a lot of attention and resources are available for innovation ('Proof of Concept'), this is much less the case for the last and most difficult phase of the innovation process, implementation ('Proof of Business'). Without this final step, there is no value creation[1]. Lack of implementation, and therefore value creation, creates growing frustration, making innovation less and less popular. Therefore, we need to look for the factors, the barriers, that stand in the way of (rapid) implementation.

As stated above, an important cause for difficult implementation of PHC is the fact that a new medical model also requires adjustment or readjustment of a large part of the healthcare system. The current healthcare system is complex, rigid and conservative and responds too slowly to innovations. We are missing out on health gains as a result. What is needed is a resilient, flexible, experimenting and learning (together an evolving) system, in which optimal use is made of all available (new) data, tools and knowledge, and applications in the field of PHC. In such a system, optimal learning from successful and unsuccessful PHC projects takes place. It is especially important to look at developments that face implementation barriers and therefore struggle with the 'Last Mile' or fail to complete it (die before the finish line).

If we fail to convert PHC innovation into value creation, we fall prey to a familiar formula:

NT+OS=EOS
New **T**echnology into an **O**ld **S**ystem results in an **E**xpensive **O**ld **S**ystem.

Within the mission of the PHC Catalyst, it fits to further explore what exactly those implementation barriers for PHC are.

The reason for this report is to map out the implementation barriers for PHC in the Netherlands. To do this we use the learning method developed by the Institute for Brilliant Failures. This method is about recognizing failure patterns, or developing 'failure intelligence'. The research consisted of desk research and field research, during which we talked to those involved in a large number of the many PHC-related projects in the Netherlands. Many recognized the challenges of the Last Mile, where their projects were delayed or even stopped for various reasons (failure patterns). Finally, several members of the PHC Catalyst Alliance were interviewed. They recognized the barriers and the failure patterns identified, but also came up with solution approaches. This again illustrates the power of the diversity of knowledge present in the alliance and the importance of combinatorial innovation to achieve the systemic changes needed for PHC to actually grow and flourish and be implemented in daily practice.

I would like to thank all those who provided input in the creation of this report, in particular Bas Ruyssenaars from the Institute for Brilliant Failures and lead author Judith van Schaik, co-initiator of the PHC Catalyst, who has tirelessly combined all the results from the research with many other sources of knowledge on the subject.

Of course, we appreciate any kind of feedback and input to continuously update and enrich this discussion document!

Paul Iske
Chairman PHC Catalyst Foundation

[1] The narrow aim of implementation is that the innovation is integrated into professional practice, into the functioning of organisation(s) or into the structure of the sector; the broad aim is that the innovation brings improvement, creates value.

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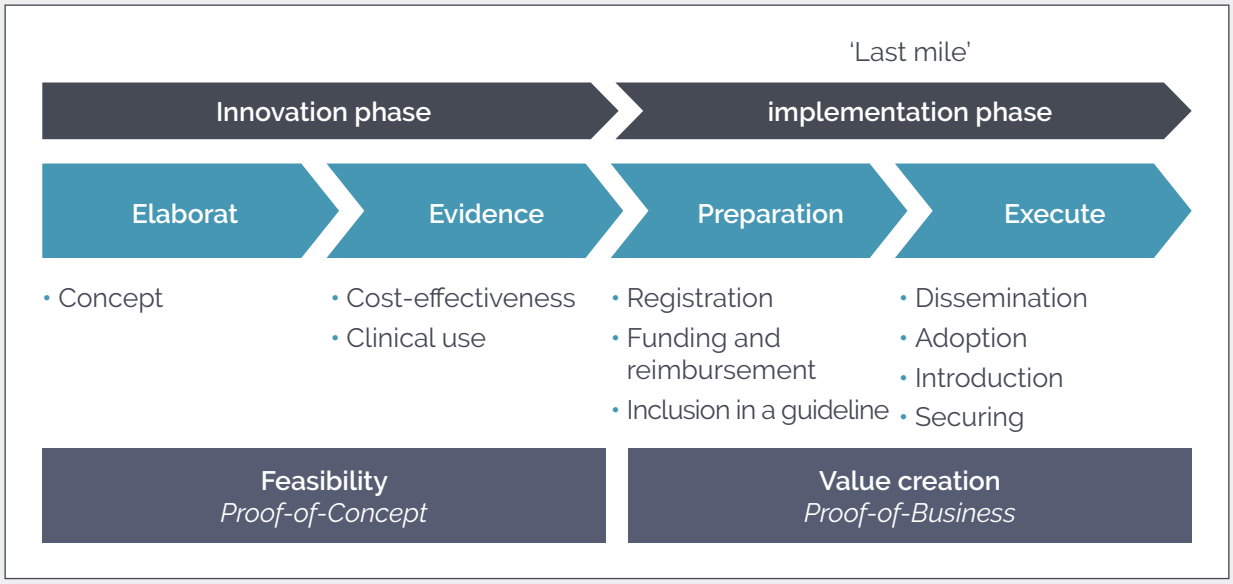
Management summary

Innovation is only innovation when it is implemented in daily practice

The PHC Catalyst Alliance's mission is to accelerate the transition to data-driven personalized care by creating a responsive PHC environment. Previous research commissioned by the PHC Catalyst Alliance has shown that by applying existing PHC solutions in daily practice, we are already gaining 3-7 additional years of life in good health. With this, the goals set by the EU can therefore already be realized in the short term.

A number of implementation barriers stand in the way of these health gains. The PHC Catalyst Alliance decided to conduct a study on the challenges for PHC. The aim of this study is to get a picture of the current status of PHC in the Netherlands, the relevant implementation barriers and how we could overcome these together.

Figure 1: 4 phases in the PHC transition process

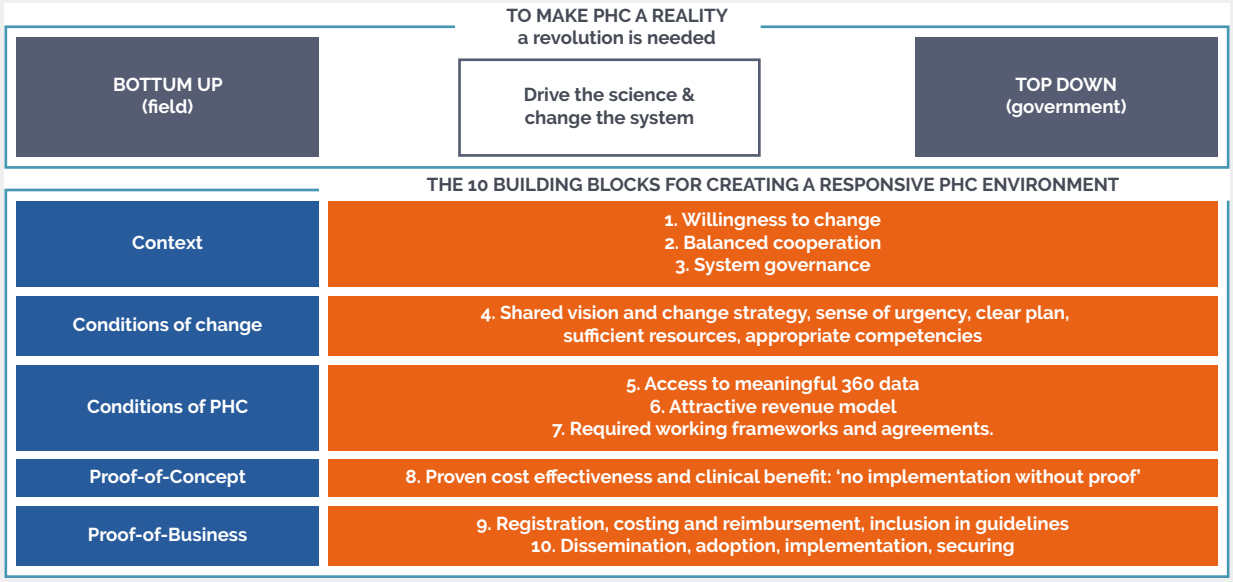


In practice, many PHC innovations enter the 'Last Mile' with an innovation phase that has not been properly completed, in the sense that cost-effectiveness and clinical utility have not been proven or have not been proven sufficiently. Although the focus of this study and the PHC Catalyst Alliance is on the 'Last Mile', we have also included this 'difficult evidence base of PHC' in this study because it is a major bottleneck for implementation: after all, 'without evidence, no implementation'.

A receptive PHC environment can be broken down into a dozen categories (building blocks), as shown in the figure below. In this figure we see a combination of bottom-up and top-down aspects necessary to initiate and accelerate the transition to PHC, as 'patients change policies and policies change healthcare':

- **Bottom-up:** Many changes are set in motion by citizens who see that the system is preventing them from making sufficient use of new opportunities. They demand policy changes that pave the way for smarter, better and more humane healthcare, such as PHC.
- **Top-down:** The government is crucial in the transition to PHC, because the government represents all citizens and the government has the main tools in its hands (laws and regulations, networks, public campaigns, financial incentives) to make the desired change possible.

Figure 2. Building blocks of receptive PHC environment



Within each of these building blocks, barriers have been reported and possible solution approaches, which are tabulated below:

Table 1. Barriers and solution approaches

Building block	Barriers	Solutions
Context		
1. Readiness to change	Old thinking	• **New perspective on health:** no longer "the average" but individual differences (variation). • **New approach to healthcare:** smarter use of limited collective resources: prevention is better than cure, hit hard & hit early, personalise where possible, radically eliminate. senseless care, promote healthy behaviour • **New way of thinking:** abundance thinking, and-and thinking: 'I see bears and the road'.
2. Balanced cooperation	Complexity: 'think big, start small, learn fast'.	• **New forms of cooperation are necessary:** with other fields, disciplines and stakeholders • **Different approach:** combinatory innovation and experimental learning
3. System control	Lack of system direction: 'the empty space at the table'.	• **System director:** management by the government.

Building block	Barriers	Solutions
Conditions for change		
4. Shared vision, sense of urgency, clear plan, sufficient resources, right competences	Absence of these five necessary conditions for change	• **Shared vision and change strategy:** make clear how the future differs from the past and how it can be achieved. • **Sense of urgency:** make (transition to) data-driven personalised care a national priority based on opportunities and threats. • **Clear plan:** make use of existing plansxvi and of parties who have committed to these plans. • **Sufficient resources:** ensure new financial flows for PHC: funding to test innovations in practice (implementation research), funding for the necessary infrastructure and the necessary financial resources for the costing and reimbursement of PHC solutions (e.g. by quickly eliminating nonsensical care and stimulating healthy behavior). • **Right competences:** use frontrunners, use successful examples, make sure curricula of medical-technical training are adapted. • **Learning strategy:** learn from all experiences, positive and negative (brilliant failures).

Building block	Barriers	Solutions
PHC Conditions		
5. Access to meaningful 360˚ data	Limited (access to) meaningful 360˚ data: Lack of good quality data, data sharing mostly limited, lack of interoperable (inter) national data infra-structure, no EPRD	• **Improve data quality:** update existing data, make sure data collected is interoperable and standardised (EPD). • **Promote data sharing:** adapt or replace the informed consent model (dynamic consent), improve opportunities to share anonymised data in the context of the public interest (donor codicil data as an amendment to the donor law, MedMij, My Data Our Health), exchange/ pay for the economic value of data (data-sharing platform), learn from data without touching them or federated learning (PHT), compulsory data sharing (HSD2 by analogy with PSD2). • **Invest in an interoperable (inter)national infrastructure:** a suitable infrastructure is needed to collect/share/combine/apply data and/or make use of linking existing databases (e.g. PHARMO). • **Commit to the creation of an online personal health environment:** where citizens can retrieve their own data from various sources, manage it and release it for research purposes.
6. Attractive earnings model	Lack of attractive earnings model where the investor also gets the benefits	• **New revenue models:** value distribution by introducing (and seeking) the right incentives in the system and forming effective (multi-stakeholder) coalitions with the right balance of scale and complexity. • **Develop a method to determine the economic value of data:** data is the raw material for new earning models 'data is the new gold'.
7. Required working frameworks and agreements	Lack of PHC policies, related laws and regulations, and standards and shared language	• **Adapt working frameworks and agreements to the new reality of data-driven personalised care:** develop necessary PHC policies, related laws and regulations, and standards and shared language.

Building block	Barriers	Solutions
Proof-of-Concept		
8. Proven cost-effectiveness and clinical benefit: 'without evidence no implementation, without implementation no innovation'.	Difficult evidence for PHC: 'application and evidence hold each other hostage, as it were'.	• **Further refine current PHC knowledge:** identify missing factors and interactions that play a role in disease complexity. • **Closing the gap between science and practice:** implementation research, feedback of practice results to research, focus on PHC applications of which the combination of target groups and improvements deliver the most value in practice. • **Create space for alternatives to build evidence in practice:** consensus needed on data collection in practice: 'instead of n-of-1 trials are relevant when Randomized Clinical Trials (RCTs) are not applicable or available, how about RCTs are relevant when n-of-1 trials are not applicable or available'. • **Diverge and converge:** Initially use PHC applications broadly to learn, so that at a later stage you can treat more effectively.

Building block	Barriers	Solutions
Proof-of-Business		
9. Registration, costing and reimbursement, inclusion in guidelines	PHC applications are mostly not reimbursed and little is included in the guidelines	• **Adapt/eliminate market admission criteria to the new reality of data-driven personalised care:** flexible/dynamic instead of rigid/static: Registration: 'rolling review' (example: Oxford corona vaccine) Access and payment while we collect additional data on effect and side-effects (example: DRUG Access Protocol) Conditional admission and reduced price during conditional admission (in analogy with rare diseases)? Shift towards early access and outcome-based payment schemes. • **Create financial space for funding and reimbursement of PHC solutions:** 'money makes the world go sustainable'. • **Encourage inclusion in guidelines, ensure quick implementation of guidelines:** optimise the input of PHC experts in working groups that draft guidelines, make guidelines a joint responsibility (multi-stakeholder guideline) and each of these parties can put the updating of the guideline on the agenda.
10. Dissemination, adoption, implementation, assurance	Unfamiliarity with PHC among patients and the general public, limited knowledge among practitioners about possibilities and applications, limited experiences and convictions for practitioners, other obstacles surrounding application PHC: "unknown makes unloved".	• **Take your time:** to come to deeper forms of understanding. • **Create narrow but deep support:** you have to learn to play chess. Place every action you take in a wider perspective (yourself, your organisation, your environment). • **Build a lobby for PHC:** use frontrunners, use successful examples, ensure adjustments in the curricula of medical-technical training, good public campaign, use various communication means and channels. • **Create room for experimentation:** to let people experience the benefits of PHC. • **Create a safe environment for people.** • **Reduce obstacles to PHC implementation.**

Roadmap to the future of PHC

Historically, system transitions take about 30 years. We don't have that time. With the current technological possibilities, it should also be possible to do this faster, as long as there is sufficient sense of urgency and focus. The ambition is therefore to have realized the 'North Star' (data-driven personalized healthcare) by 2030. What is needed to realize this ambition is a collaborative approach aimed at ensuring that existing and future PHC solutions quickly reach daily practice and can be deployed nationwide.

To achieve the desired rate of change, we have created a pragmatic roadmap based on John Kotter's change methodology.[i]

- **Step 1. Create a sense of urgency:** make (transition to) data-driven personalised care a national priority.
- **Step 2. Gather a leading coalition:** public-private partnership.
- **Step 3. Appoint a director:** for example, the government will direct this cooperation to make it productive.
- **Step 4. Appoint a management team:** PHC Catalyst Alliance makes itself available to carry out direction activities together with partners.
- **Step 5. Develop a shared vision and a change strategy, and draw up a clear plan of action:** see for example the 'PHC National Action Plan'.
- **Step 6. Communicate about the intended transition to PHC:** create support by using frontrunners and successful examples, adaptations in curricula of medical-technical education, good public campaign, use various communication tools and channels.
- **Step 7. Make it possible for others to act:** remove structural barriers and provide the necessary competences and resources.
- **Step 8. Generate short-term successes:** sprint with flagship projects.
- **Step 9: Keep up the pace:** increase pressure, increase pace, and expand acceleration projects.
- **Step 10. Create a new culture:** choose development goals, make it fun, and arrange support.

Conclusions

- The health care system is increasingly bogged down;
- PHC offers the opportunity to make healthcare more sustainable: 'more patient benefits at less cost to society';
- Frontrunners (e.g. PHC Catalyst Alliance) are taking matters into their own hands and forming a movement through 'connecting the dots' to accelerate the transition to PHC;
- We know from past transitions that it takes about 20% of the population to irreversibly change a system;
- Transitions almost always start from the bottom up, because politics and government are slow to change;
- In addition to this bottom-up initiation from the field, a top-down movement is also needed.
- The government must develop a vision of the new desired system, give it direction and change with it. In doing so, the government may not be able or willing to carry out the necessary transition to PHC itself, but it can slow it down or speed it up;
- It can accelerate the process by creating conditions, removing institutional obstacles, establishing links between initiatives and providing the necessary resources and competencies;
- The guiding principle for change must be: 'Just do it'. Experiment, learn, and do it better.
- Netherlands, ask yourself: do we want to be leading or suffering?
- Remember that success is not limited to improving healthcare in the Netherlands, but that it gives Dutch entrepreneurs the opportunity to market this new form of healthcare outside the Netherlands. Health as the new Wealth'.

1. Introduction

- People want affordable healthcare that is tailored to the individual as much as possible;
- To achieve this, a completely different view of health and healthcare is needed (**see Appendix 1 and 2**);
- PHC plays a leading role in this development. With PHC we make healthcare smarter, better, more human and cheaper: 'more patient benefits at less cost to society';
- By using PHC, we can gain 3-7 extra years of life in good health;
- A number of barriers stand in the way of these health gains;
- In this study, we look at these implementation barriers to PHC;
- It is (high) time for collective action to realise the value of PHC.

The Dutch healthcare system is in a state of flux. From standard treatment for everyone, we are moving towards care that is specifically tailored to the characteristics and preferences of the individual. This personalised care (PHC) is also called *precision medicine*.

The increase in knowledge in the biomedical field (systems biology, systems medicine) combined with an unprecedented revolution in the field of Big Data[2] & AI has[3] created a 'perfect storm', which has accelerated the transition towards PHC: more and more precise diagnosis and treatment options are emerging, focused on individual patient characteristics and preferences. The problem is that the healthcare system lags behind these technological developments, with the result that PHC innovations do not reach practice sufficiently.

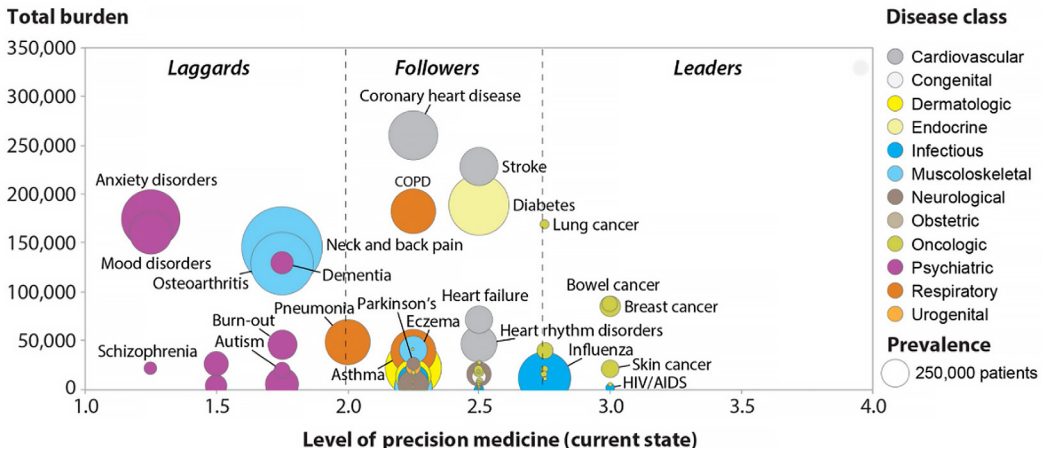
In the study '**n=1, a new paradigm**'[i][ii], the PHC Catalyst ism Gupta Strategists investigated what the potential health gains would be if we were able to use these technological innovations in the field of PHC more widely.

This research shows that we can gain 3-7 extra life years in good health by applying existing PHC solutions in daily practice. Oncology and infectious diseases are the leaders in the field of PHC ('leaders'), followed by chronic diseases such as cardiovascular diseases, rheumatism, diabetes, COPD ('followers') and neurological and psychiatric diseases and back and neck pain are the laggards.

[2] The revolutionary power of big data (many, fast, diverse) lies in combining a multitude of different data, enabling more personalised approaches.
[3] AI = artificial or rather additional or augmented intelligence.

Figure 3. Extent to which PHC is applied

Current level of precision medicine versus total burden of disease in the Netherlands
[PM score (x-axis), total DALY in The Netherlands in 2017 (y-axis) and prevalence (size)]



A number of barriers stand in the way of these health gains. In this study, we look more closely at these implementation barriers to PHC.

2. PHC, a new medical model

2.1 Definition

PHC is a relatively new concept, and there is no universally accepted definition yet. The PHC Catalyst uses the following definition for personalised healthcare:

> "PHC is a person-centred health paradigm where prevention, diagnosis, treatment and monitoring are based on relevant biological, environmental and behavioural characteristics of the individual."

The term PHC is used for different perspectives:

- In its entirety, PHC is an *integrated care approach* that uses genetic characteristics, lifestyle factors, social factors and environmental factors of an individual for prevention/screening, diagnosis and therapy.

- A narrower perspective concerns *pharmacotherapy* based on genetic and other characteristics of a patient (also called 'personalised medicine' or 'precision medicine'). This narrower approach in particular is currently being applied in practice.

Some associate PHC with expensive healthcare or healthcare for the rich, where doctors identify risk or tailor treatment based on the patient's genome and big data analysis. But PHC can and should start at a much more fundamental level: PHC can begin with the use of simple (digital) tools to help people gain insight into their own health situation, or to help general practitioners collect basic information in a simple and standardised way, or to dose medicines more accurately based on weight or on drug concentration in blood (individual pharmacokinetics: absorption, distribution, excretion).

Even in its most basic form, PHC increases efficiency and improves outcomes. And for the more innovative applications, such as advanced diagnostics (-omics) and personalised treatments, the cost of innovation usually decreases rapidly due to increased use and competition[iii].

2.2 Precision, precision, precision

PHC integrates data from different sources to gain new insights into disease and health, and then translate that knowledge into relevant prevention/screening, diagnosis, treatment for the individual. Precisely the right and sufficient care for each individual patient. If desired, patients can be provided with continuous information about their own health in order to make well-considered choices from as many effective and affordable interventions as possible. Interventions with an optimal result, a minimum of side effects, at minimal costs, in line with the patient's own way of living and thinking, as close to home as possible.

The new insights into illness and health allow medicine to develop further:

Precision in diagnosis: better characterisation of diseases

Better characterisation of diseases

- Since the breakthrough of the Human Genome Project in 2001, there have been high expectations of the use of genetic characteristics of individuals for healthcare. However, it is becoming increasingly clear that in order to better characterise disease, other data (clinical, biological, lifestyle, psychological, socio-economic etc.) are required in addition to genetic data: 'nature and nurture'.
- Genetic information is only one part of the puzzle in tackling disease. In addition to DNA ('the genome'), there are several so-called 'uncles' that determine the uniqueness of an individual: transcriptome, proteome, metabolome, microbiome, epigenome, physiome, and exposome; the DNA is 'the library' where the information is safely stored and an individual carries this information with them throughout their life in every cell in the body, but the other 'uncles' are constantly changing. They say more about the current status of the individual and his health, but are more difficult to determine and have only temporary validity.
- When more information from the (whole) genome and other data is linked to medical knowledge via ICT, we can better (re)classify diseases, so that tailor-made therapy can be applied. Moreover, it can become clear how we stay healthy. In this way, healthcare becomes more efficient, better and cheaper.
- It is no longer a question of diagnosing predefined syndromes (e.g. asthma), but of a finer staging of diseases (a 'handprint' of different biomarkers and clinical characteristics) that together should say something about the subtype of the disease (different profiles of asthmatics) and the expected course, and also about the clinical effectiveness of different therapies. Moreover, these analyses should reveal new targets for better medicines.

Precision in treatment: customised treatment based on the individual's unique characteristics

Mass medicine stratified medicine ▸ personalised ▸ medicine individualised medicine ▸
As the unique characteristics (*nature*: DNA) and circumstances (*nurture*: environment, behaviour) of the individual are taken into account, screening/prevention, diagnosis, and treatment become more personalised and ultimately individualised.

Precision in healthcare: making care more sustainable by shifting from sickcare to healthcare

Symptom management ▸ treat underlying cause & prevent disease
Shift from symptom management to treating the underlying cause and preventing disease. From (unsustainable) sickcare to (sustainable) healthcare.

2.3 The value of PHC:

Important starting point for realising sustainable health care.
PHC creates value for the individual, society and the economy:

- **More patient benefits:** more precision leads to better screening/prevention, diagnosis, and treatment so people can age more healthily (less overtreatment and undertreatment). Research shows that by broadly applying existing technological innovations in the field of PHC, we can already gain 3 to 7 extra years in good health.
- **Less cost to society:** more precision also leads to less waste, which contributes to cost control. Although there is a perception that PHC is costly, in reality it leads to smarter choices and better outcomes for both the patient and the system in the longer term.
- **Innovation as a driver for economic growth:** knowledge drives innovation, innovation is the engine for job growth, and high-paying jobs in the Life Sciences & Health sector (LS&H) make an important contribution to economic growth.

2.4 PHC in high gear

Although the concept of personalisation is not new, the first targeted therapies targeting a unique characteristic were adopted over 20 years ago, recent medical scientific developments (systems biology: -omics) and technological advances in data storage and computing power of computers (Big Data & AI) and the increasing use of electronic health records (EHR) have accelerated the possibilities of personalisation. We are still relatively at the beginning of developments in the field of PHC, but now that we are at an inflection point, developments will only accelerate. A tsunami of PHC innovations awaits us.

More personalised medicines in development
The share of personalised medicines in the pipeline continues to increase. Using biomarkers in blood or tissue and/or organoids, it is increasingly possible to determine in advance whether a medicine will be successful. Sometimes a medicine can even be tailor-made for a patient, for instance in the case of cell or gene therapy. It is estimated that cell and gene therapies can tackle 45% of all diseases.
Since 2009, EMA has authorised 12 cell and gene therapies. The question is whether these therapies will reach patients in the Netherlands. Cellular and gene therapies (or more generally: personalised medicines) are so different from conventional medicines that they are pushed to the limits of the current market authorisation system. The tenability of this system is therefore under discussion.

Table 2: Current vs. desired system situation

Current system situation	Desired system situation
Biomedical science and data science are too disconnected	Medicine uses data science, advanced analytics, and technology
The sharing of data in healthcare is not well possible due to inadequate standardisation, IT infrastructure, and legislation and regulations and their misinterpretation	A suitable infrastructure for collecting, sharing, combining, and applying data
Collected data and acquired knowledge are not shared due to conflicting business models	Collected data and acquired knowledge are shared and contribute to the development of knowledge about disease and health at a population level based on a common value case
Thinking and acting is based on 'the average' (one-size-fits-all)	Thinking and acting based on unique (biological) characteristics of the individual (customisation)
Treatment of disease is mainly aimed at treating symptoms ('trial and error' medicine: too much 'sickcare')	Approach aimed at unravelling underlying biological processes that cause functional impairment (systems medicine: healthcare)
Market authorisation system grafted on 'the average' (RCTs, registration, reimbursement, professional group guidelines)	Market authorisation system based on 'the individual' (n-of-1 trials, rolling reviews, early access and outcome-based payment models, multi-stakeholder representation in guideline committees)
Professional group insufficiently familiar with PHC	PHC subject in education and professional development
The public is insufficiently informed regarding the opportunities and barriers to personalised care	Citizens/patients are aware of the opportunities and challenges of personalised care and their own role; Citizens/patients are (continuously) provided with reliable information on their own health in order to make informed choices.
Application of innovation is hampered by the current organisation of care	Innovation quickly finds its way into daily practice through receptive care environment

3. Implementation barriers for PHC

- Technologically, the transition towards PHC has accelerated: there are more and more diagnostic, treatment and monitoring options focused on individual patient characteristics;
- However, the problem is that the healthcare system lags behind these developments, with the result that innovations do not sufficiently reach practice;
- To make PHC possible for the growing number of patients with chronic diseases, a revolution is needed, both in the acquisition of knowledge and in the organisation of care.
- In addition to heavy investments in a solid data infrastructure, in making large amounts of high-quality data available, and in technological and methodological developments, knowledge coalitions and intensive contact with society are indispensable.
- The success of PHC depends on the coordinated efforts of parties, the mobilisation of sufficient resources (data, knowledge, time, and money), and the scale of projects to generate impact.

3.1 Science runs faster than its frameworks

Profound advances in science, data, analysis and digital technologies make it possible to provide care that is tailored to the unique characteristics and preferences of the individual. But with the new developments in the field of PHC, mainly research is done, the implementation in daily practice lags far behind. Only a fraction of humanity receives personalised care. Healthcare systems struggle to implement and apply new PHC innovations. Therefore, the PHC Catalyst Alliance decided to conduct a study on the challenges for PHC. The aim of this study is to get a picture of the current status of PHC in the Netherlands, the relevant implementation barriers, and how we could overcome these together.

PHC Catalyst Alliance
The Alliance would like to contribute to accelerating the transition to PHC by creating a receptive environment. We will start by accelerating what is already there: because if we do not succeed in making existing PHC applications available nationwide quickly, how can we cope with the tsunami of PHC applications coming from the pipelines of innovative companies?

For more information on the PHC Catalyst Alliance, please see the policy plan on the website: https://www.phc-catalyst.nl

The research was carried out by the Institute for Brilliant Failures, which applied a method for recognising and learning from patterns of failure. This makes it possible to identify and describe underlying factors that stand in the way of the (rapid) implementation of care innovations.

3.2 Challenges for PHC

3.2.1 Exploratory research approach

- **Global overview:** Initially, desk research was used to obtain a global overview of PHC-related initiatives in the Netherlands. The conclusion was that hundreds of PHC-related initiatives could be identified in the Netherlands;
- **Top-of-mind initiatives:** Next, experts were interviewed from different fields. This resulted in 36 top-of-mind PHC-related initiatives (**see Appendix 3**);
- **Initiatives we can learn from:** PHC Catalyst Alliance members were then asked which of these 36 top-of-mind initiatives have the most impact for patients; what can we learn the most from? The result was a list of 12 initiatives, all of which had gone beyond the start-up phase and had already been learned from.

Table 3: 12 selected initiatives

Project
Diagnosis/genomics + personalised treatment plan:
1. MammaPrint (breast onco)
2. DRUP study (access targeted therapy for out-of-treatment patients)
3. Ciro (chronic lung)
4. IHCH service regarding prevention, genomics (23andme.com) and precision medicine
5. Spiro nose / e-Nose (lung diseases)
Personalised treatment:
6. Care@Home / home delivery (oncology)
7. MediMapp (insight into personal care pathways in oncology, rheumatism, MS
Personalised recovery, monitoring & coaching:
8. HartWacht (home monitoring of heart patients)
9. DigiCoaches / MyIBDcoach (coaching IBD)
Prevention:
10. IHCH Healthchecks (provider of gynomic counselling, precision medicine)
11. Nutrikliniek (test for genetic predisposition to obesity, diabetes, etc.)
Entire customer journey:
12. HealthSuite Philips/Salesforce (cloud-based platform clinical and other data).

- These initiatives were therefore further analysed, by means of desk research and interviews with experts involved or aware of these initiatives, and were used to identify relevant implementation barriers and possible solution directions.

Guideline interview questions for experts

a What initiatives do you know (were/are running) in the field of PHC in NL?
b What phases can be distinguished in initiatives?
c What categories are there?
d What is your estimate of the number of PHC-related initiatives and their size?
e What barriers do you find in practice?
f In what order did the barriers take place?
g To what extent did the barriers take place?
h Which barriers do you think are most dominant in NL at which stage?
i What steps were taken to remove the barrier(s)? And what was the result?
j What were the Moments of Truth (crucial interactions) and go/no go moments?
k What would you do/not do next time, who would you involve/not involve?

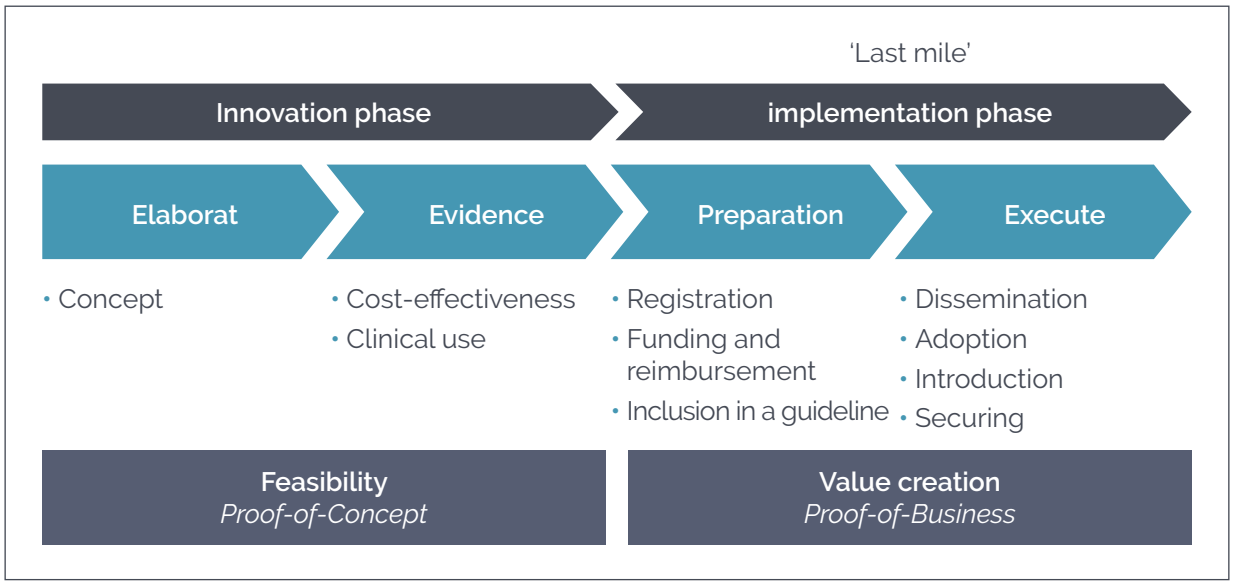
3.2.2 The current status of PHC in the Netherlands

The transition to PHC is still in its early stages, as elsewhere in the world. However, there are signs that the transition is gaining momentum. The emergence of strategies, plans and policies to enable PHC suggests that stakeholders are not only thinking about how to improve care for citizens ('more patient benefits'), but also how to build future-proof healthcare systems ('at less cost to society'). The increased acceptance of key technologies such as whole genome sequencing, EHR, (real-world) data registries, and AI illustrates a shift towards PHC.

3.2.3 The phases in the PHC transition process

The study revealed that the PHC transition process can be divided into four phases. The implementation phase is also referred to as the 'Last Mile'.

Figure 1: 4 phases in the PHC transition process.

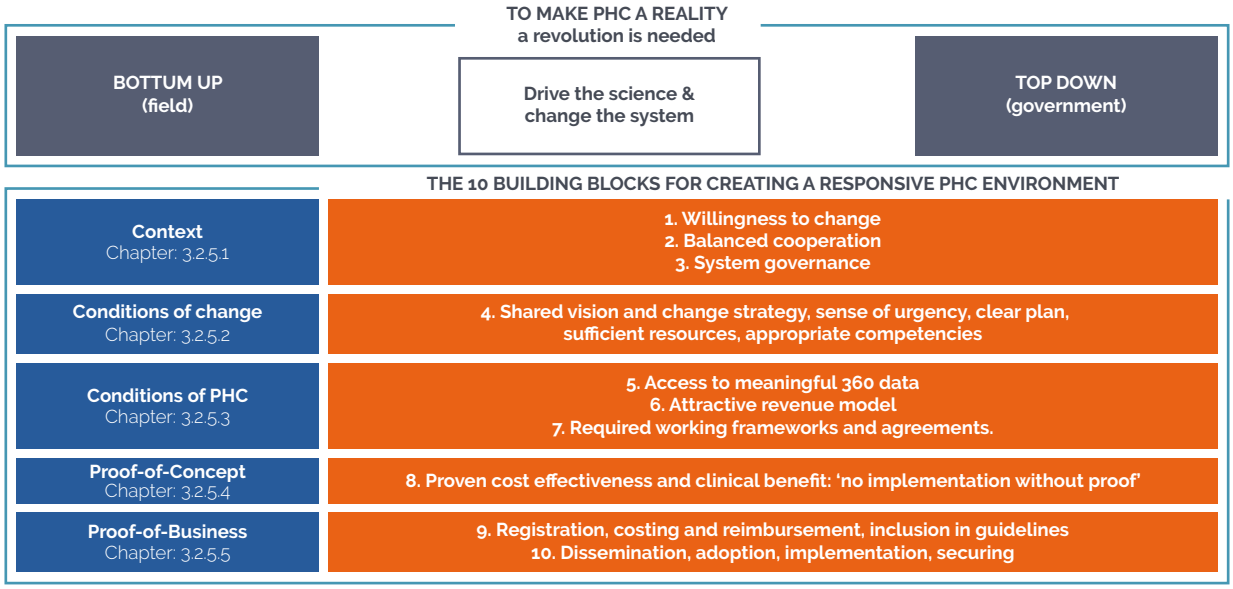


Our research shows that many PHC innovations enter the 'Last Mile' with an innovation phase that is not well completed, in the sense that cost-effectiveness and clinical utility are not or insufficiently proven. Although the focus of the PHC Catalyst Alliance is on the implementation phase ('Last Mile'), in our study we also included this 'difficult evidence of PHC', as this is an important bottleneck for implementation. After all, 'without evidence, no implementation'.

3.2.4 The building blocks of a receptive PHC environment

The research showed that a receptive PHC environment can be divided into ten categories (building blocks):

Figure 4: Building blocks of receptive PHC environment



Barriers have been reported within each of these building blocks, many of which can be related to 'Archetypes for Brilliant Failures' as developed by the Institute for Brilliant Failures (**see Appendix 4**).

Archetypes are 'universal lessons' (failure patterns or learning moments), which transcend a specific experience and are also applicable to many other innovation projects. They have emerged from the analysis of a large number of Brilliant Failures and have been developed to stimulate reflection and learning: '*recognise, acknowledge, experiment, learn, change*'.

3.2.5 The implementation barriers and solution options

3.2.5.1 Context: Building Blocks 1 - 3

Building Block 1: Change Readiness

Barrier: Old thinking

The canyon

Ingrained patterns

In our lives, we often encounter the same situations. In order to deal with them efficiently we develop routines, habits and best practices. Both individual as organised, we learn skills and these become ingrained in our brains or in the form of written and unwritten protocols in the organisation or society.

- **PHC calls for a new approach to health (see Appendix 1):** PHC calls for a completely different approach to illness, patients and data. This starts with the fact that we no longer look at the greatest common denominator ('the average' is central), but that we become curious about the individual differences between patients. So, 'the variation' is central, a new way of looking at health.

- **PHC calls for a new approach to healthcare (see Appendix 2):** prevention is better than cure, hit hard & hit early, personalise where possible, radically cut out nonsensical care, and promote healthy behaviour.

- **PHC calls for a new way of thinking in general:** we are not in an era of change, but in a change of era -from the industrial era to the digital era-, which will transform our country in the next 20 years into a society in which the balance of power and ways of working have been radically turned upside down (see chapter 5, 'Nederland kantelt'). We see this development of radical system innovations and transformative reforms in all sectors, and it is accompanied by a new way of thinking:

Table 4: Required shift in mindset

Industrial era	Digital Age
Scarcity thinking	Abundance thinking
Distrust	Trust
Control (Planning)	Space (Experimental learning)
Efficiency	Attention and time
Rules	Freedom of choice
Cost-benefit	Quality and affordability
Silos / scattered stand-alone approaches	Multi-stakeholder cooperation
Shareholder value	Stakeholder value
Fixed thinking: or-or thinking *I see bears on the road*	Thinking backwards: and-and thinking *I see bears and the road*

The most important resistance to innovation is a reluctance to change: healthcare is the most conservative market there is. Change and renewal take a very long time. Even when the cost-effectiveness and clinical benefit of innovations have been proven, it often takes years before they are applied in daily practice on a national scale.

This has several causes:

– **Unique features of the healthcare market:** healthcare is the only sector that has a complete separation of stakeholders that determine value: the health insurer pays the value, the patient benefits from the value, and the doctor prescribes the value. In other sectors, this is usually united in one and the same stakeholder: the one who purchases the product is also the one who pays for the product and benefits from the value.

- **Conservatism among doctors:** the most important principle in medical ethics is non-damage ('primum non nocere' or 'first do no harm'). This principle of non-detriment asks doctors not to perform actions that are harmful. In medicine, the expression 'it doesn't do any good, it doesn't do any harm' does not always apply. For example, you can harm someone with an unnecessary operation or too much chemotherapy. Doctors are therefore quick to think 'what's good is good' and 'what's proven effective, we should keep'.

- **Lack of successful examples:** PHC is a field, which is still under development. Examples do exist, such as biomarkers that can predict whether a medicine will be successful in a patient, or CAR-T cells that enable a completely individual treatment, but these examples are limited and are mainly found in the field of oncology, which leads the way in PHC. Because authorisation and reimbursement are not yet properly regulated, successful PHC applications do not reach the patient, so that these examples are not visible.

- **Few incentives for caregivers to change:** System transitions also require personal transitions. Many care providers spend a third of their time filling in forms. They feel they are stuck in a rigid and bureaucratic system that does not honour their own initiative. In addition to regular patient care (business-as-usual), there is little time or mental space left for personal mentality change (focus on the variation instead of the average) and large-scale innovation implementation.

Solution building block 1: **Promote new thinking ('the variety' central) by increasing the capacity to change and reducing resistance to change**

- In order to change healthcare, it is important to create support among practitioners. Leaders set the tone. Let them involve and convince the professional group with successful PHC-examples that give something to hold on to and are directly applicable in daily practice. Combine this with incentives to change.

Building Block 2: Balanced cooperation

Barrier: **Complexity**

- **PHC, it's more than complicated:** PHC is complex and evolving, and the healthcare landscape in which PHC must land is also complex and overburdened. The transition to PHC requires the commitment of many parties and disciplines. Who takes the lead? Where do you start? How do you approach it?

Complex issues require a unique approach
There are different types of problems: simple problems, complex problems, and complex issues. Each has its own unique approach and process. We can all solve a simple problem, alone or in a small group. Complex problems require expert knowledge or skills and the use of problem-solving strategies. You have a simple or complex problem at hand if you know there is a (technical) solution. With complex issues, the problems do not stand alone. They interact with each other because they are part of the same dynamic system. Complex issues are characterised by the fact that they have no immediately visible cause-and-effect relationships. This makes it impossible to find unequivocal solutions; there is no 'one-size-fits-all' solution. The fact that everyone looks at the issue differently and values it differently contributes to this. Only with a common vision and small experiments can you navigate through such complex issues, always taking into account new developments from outside. The best way to do this is with a diverse group of people and organisations that are involved and want to commit to the issue. People who have the knowledge and energy to work on it together and the ability to deal with their differences. But they also have the patience and discipline to take small steps and learn from the results.

Solution direction building block 2: **new forms of cooperation ('combinatory innovation') and a different approach ('experimental learning') are needed to solve the complex PHC issue**

- **New forms of cooperation ('combinatory innovation'):** To accelerate the transition to PHC, it is necessary to map out all the perspectives of parties who jointly form the complex care system.

Elephant

The whole is more than the sum of its parts
Sometimes things only become clear when you look at them from various angles and when you combine observations from various perspectives. This principle is beautifully expressed in the parable of the elephant and the six blindfolded people. These observers are asked to touch the elephant and describe what they think they feel. One says a 'snake' (the trunk), the other a "wall" (side), another a "tree" (leg), yet another a "spear (tusk), the fifth a 'rope' (the tail) and the last a 'fan' (ear). None of the participants describes any part of the elephant, but when they share and combine their observations and combine them, the elephant 'emerges'.

It is the same with solutions that are sought to accelerate the transition to PHC and to remove barriers. Usually, these solutions only 'appear' when all relevant parties are involved. In complexity theory, this phenomenon is called emergence. The following stakeholders play a role here: (a) patient/citizen, (b) care provider, (c) scientist/researcher, (d) management of care/knowledge institution, (e) payer/health insurer, (f) government/politics (g) quality guards (h) supplier/company.

Each stakeholder is looking for its own value case ('What's in it for me?') and therefore sets its own priorities. For example, the patient puts his own health first, while companies have to make a profit and scientists want to strengthen their knowledge position (**see Appendix 5**).

The *collective* value case arises through value exchange between the stakeholders. This multi-perspective (360o) value proposition reflects the complexity of the playing field. To accelerate the transition to PHC, we therefore face the challenge of 'how to maximize the collective value case' and 'how to resolve individual and conflicting differences'. Sometimes compensation from the collective is needed to achieve an acceptable 'win-win'.

The wrong wallet

One person's advantage is another person's disadvantage
In complex situations, it is sometimes difficult to estimate where the advantages and where the disadvantages of a project occur. It regularly happens that the change is positive for the system as a whole (a savings, better service, better public health), but at the expense of one or more parties within the system. When it comes to money, compensation from the collective is sometimes necessary to achieve an acceptable, win-win (or not lose-not lose) situation, where the wallet of one is not filled by that of the other.

Many of the challenges we face within PHC are not unique to the Netherlands ('our healthcare systems may differ, but the challenges are the same'). It therefore makes sense to (also) cooperate internationally within European and global partnerships.

- **A different approach ('experimental learning'):** progress does not usually follow a straight line. The literature shows, for example, that there is no single best way of implementing because it depends on many environmental factors. PHC is complex, new and evolving. Therefore, we will have to experiment to discover the most effective and efficient way of implementing PHC. However, the current healthcare landscape is strictly protocol-driven and offers little room for experimental learning.

The light bulb

The Experiment - *'If we knew what we are doing, we wouldn't call it research'*
Progress does not usually follow a straight line. Therefore we have to try, experiment and learn to find the best approach or the right route. We also don't always have all the information or the situation is complex, so not all relevant matters and interrelationships can be known and can only be found through trial and error.

Building block 3: System management

Barrier: Lack of direction


The empty place at the table

Not all relevant parties are involved
For a change to be successful, the agreement of all relevant parties is needed. If one party is missing in the preparation or implementation there is a good chance that, due to a lack of involvement, that party is not convinced of the usefulness or importance of the change. The feeling of being excluded can also lead to a lack of cooperation.

- **Lack of government control:** Many parties cite the lack of government control as a major impediment. The government seems to leave the transition to PHC to the market.

Directing, new core task of government[iv]
The simple model that the government makes and implements policy is no longer applicable in this day and age. Complex issues (such as making health care more sustainable) require an entirely different role and activity from the government. These issues require an intensive and equal cooperation between society and governments, whereby the government takes an explicit governing role based on servant leadership to make the cooperation productive. This concept of 'directing without power' has, for example, already been applied very successfully in the approach to 'Loneliness in Amsterdam'.

Solution direction building block 3: Government control

- **The government is the most appropriate party to take the lead,** since the government (alone) enjoys the confidence of all parties (because it has been democratically elected) and has the instruments to effectively steer the cooperation between society and governments (laws and regulations, financial incentives, public information).

  In this context, the statements made by Dianda Veldman, Director of the Dutch Patient Federation, in a recent interview are also very enlightening:

Healthy living is a matter of course in 2030[v]
What can we learn from the past government period, what really needs to be changed?
We see that the market cannot solve everything. Sometimes a strong party is needed to take control. That may be the case with the availability of medicines, but also with the introduction of the right care in the right place. If, for whatever reason, the parties in the field are unable to reach an agreement, the government must take responsibility and take the lead.

What role can the government play?
The government must actively steer where things get stuck. And facilitate a lot at the same time. We want people to be able to take control of their own health, to be able to keep track of how they are doing in a personal health environment. That is where we can make progress in the coming term of office.
Everyone living healthily for five years longer in 2040 - how do we get there?
As far as we are concerned, we don't have to wait until 2040. 2022 is also early enough for us. This can be done by cleverly responding to new initiatives in healthcare, through good prevention and information and by giving people more control over their own lives and health. Good, affordable and appropriate medicines can play a role in this.

3.2.5.2 Necessary conditions for change: Building block 4

Building block 4: Shared vision, sense of urgency, clear plan, sufficient resources and appropriate competences

Barrier: **Lack of shared vision, sense of urgency, clear plan, sufficient resources and appropriate competences**

Table 5: five necessary conditions for change

Vision	Urgence	Plan	Resources	Competencies	=	Change
	Urgence	Plan	Resources	Competencies	=	Confusion
Vision		Plan	Resources	Competencies	=	Weerstand
Vision	Urgence		Resources	Competencies	=	Chaos
Vision	Urgence	Plan		Competencies	=	Frustration
Vision	Urgence	Plan	Resources		=	Fear

Borrowed from Root people (2013) and Fleuren et al. (2012)

This diagram is borrowed from Knoster et al. (2000), who in turn drew on the ideas of Ambrose (1987)

- **Vision: lack of a collective image of the PHC future**
  The value of PHC, namely realising sustainable healthcare, is seen and endorsed by the leaders, but there is still a lack of a widely shared vision.

- Lack of sense of **urgency**

  – **Low acceptance among healthcare providers:** While there are a number of enthusiastic frontrunners in the medical community, many of whom have close ties to translational research, the vast majority are unfamiliar with PHC, the opportunities and challenges of PHC, and the systemic transition that PHC will bring about.

Inadequate dissemination of knowledge about PHC means that PHC is not sufficiently recognised ('unknown makes unloved'). Systems biology and systems medicine, data sciences, advanced analytics and technology are not part of the curriculum. In January 2020, Erasmus MC and TU Delft took a first step in the right direction by starting a far-reaching collaboration[vi]:

EUR and TU Delft: health and technology eco-system
Erasmus University and TU Delft, together with Erasmus MC, want to create an ecosystem in which top scientists from various disciplines integrate their knowledge, expertise and research methods to make new discoveries and come up with smart solutions that make healthcare more effective and efficient, improve health and quality of life and enable people to manage their own health from a distance from the hospital. The HealthTech Campus planned in Rotterdam will physically provide space for scientists from medicine and health sciences, technical sciences
and social sciences, among others, to work together with companies and institutions in start-ups, scale-ups and wet labs.

"Our healthcare system is facing major challenges, including social inequalities in disease burden and life expectancy, increases in sick life years and costs, and ever-increasing shortages in the labour market," said Ernst Kuipers, Chairman of the Board of Governors of Erasmus MC. "Without joining forces, we will not be able to find solutions to these challenges. Those solutions require maximum convergence of our knowledge and skills."

The unfamiliarity with PHC applies not only to healthcare providers, but also to other stakeholders in the healthcare system, such as health insurers and politicians. Here too, there is a handful of frontrunners and a 'big gap' with the 'first followers'.

- **Citizens little involved:** PHC is also unknown among the general public. There is a lack of public campaigns and public information. Citizens have a great influence on political decision-making, because 'patients change policies and policies change healthcare', but the citizens are not involved.

Patient change policies and policies change healthcare
When looking for a possible system owner, you ultimately end up with the person for whom we are doing it all: that is us, the citizen, the patient.
When the citizen sees what is possible but not yet offered, questions will arise. Why is this not possible, why am I not receiving the best care that suits me, why are we not making better use of all the possibilities, all the data, that are available? And with this pressure, the pressure on adapting the system will also increase and parties will have to start moving.
This pressure is increasing on the basis of the following developments, which are noticeable to all:

- A wave of new technologies is coming. We are now at the point where the impact of these technologies becomes visible around us.
- It is now no longer just a question of sketching images of the future, but of making concrete investment decisions in order to take steps. This means that organisations must have, or soon will have, a clear picture of the opportunities and threats that these technologies actually bring.

- It is therefore important that there is a certain degree of freedom for enterprising healthcare institutions to test innovations in practice. An enterprising hospital that starts an innovation takes a risk that may have a negative financial and economic impact, but also brings with it new knowledge and experience that can be put to good use at a later stage. After all, sometimes an innovation that later, in a modified form, turns out to be a great therapeutic application has a difficult start.
- The last forty years have seen countless examples of costly medical technology investments that have led to a breakthrough. Initially, they only made their appearance in university hospitals, but a decade later, in almost every hospital. Widespread adoption and competition ensure that the initially high costs of innovation are rapidly reduced.

"There is always room for improvement in medicine. In the case of medical technology, it must lead to an increase in treatment options, better quality of care or lower costs. It is important that there is sufficient freedom (time, money, manpower) for enterprising healthcare institutions to test innovations in practice".

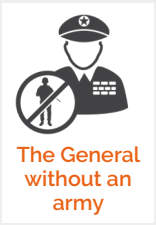
- **At the moment, there is mainly a push from technology (suppliers):** but there is no pull from the citizens, patients, and healthcare providers or a push from the government.

- Plan: lack of a national PHC policy with clear objectives
  As a result, there is also no steering of stakeholders from this shared ambition, and no translation into concrete implementation agreements.

- Resources: lack of resources (data, knowledge, money, time)

  - **Money:** to get PHC implemented in daily practice, large investments are needed in infrastructure, implementation research, and for the funding and reimbursement of PHC applications: 'de cost gaet voor de baet uyt'.

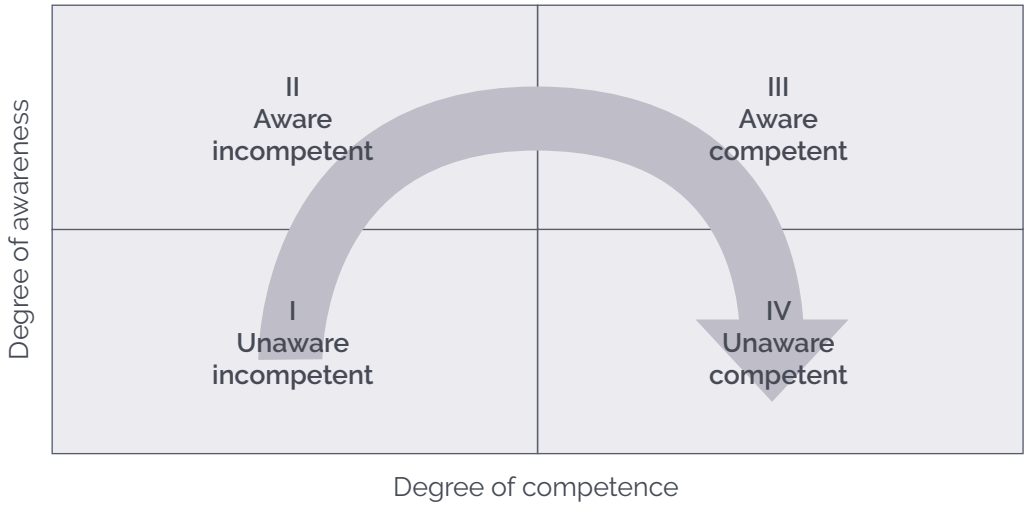
  - **Time:** Care providers have insufficient time and attention for implementation of PHC innovations within the current care system. The PHC tailor-made approach differs strongly from the current 'one-size-fits-all' approach of organisations, which makes it difficult to integrate PHC into the busy daily practice.


The General without an army

The right idea but not the resources
In order to achieve (planned) success, it is important that the necessary resources are available. These can be money, the right tools, knowledge, time, employees, partners, customers, infrastructure, etc. The person who makes these resources available must give sufficient commitment to the performer of the activities.

- Competences: new knowledge and skills are required as well as improved digital literacy.

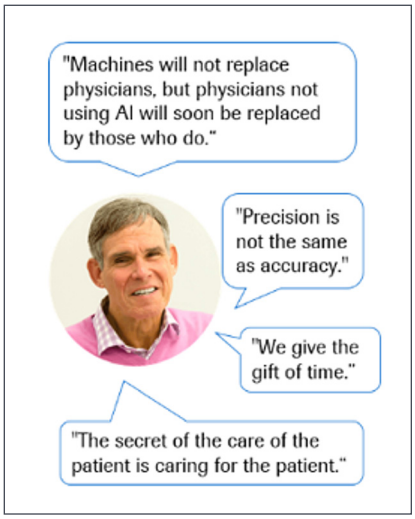
  - **Caregivers:** Successful integration of PHC in the workplace requires highly committed and trained staff. The level of PHC awareness and PHC competence among caregivers is limited (stage I or II). There is still a world to be won here.



See in this context also the education report of the PHC Catalyst Alliance ism PNA Group: 'Building, organising, and internalising knowledge about PHC'[vii].

The core domains for PHC are: (1) systems biology and systems medicine, (2) advanced diagnostics (-omics, microbiome), (3) medical imaging, (4) personalised treatments, (5) data science & bioinformatics, (6) legal and ethical.

- **Citizen/patient:** The general public is also little aware of PHC. Public education is needed to make them aware of already available PHC options.



The Topol Review[xix]**:** Preparing the healthcare workforce to deliver the digital future

Solution building block 4: **Develop a shared vision and change strategy, make data-driven personalised care a national priority, make use of existing plans such as those of VNO-NCW/MKB-NL, provide sufficient resources, ensure education and training of care workers and good public information.**

- **Vision:** develop a shared vision of the PHC future

Only by taking into account the different perspectives of relevant stakeholders can you arrive at a shared vision and a healthy business model that is viable for all stakeholders.

- **Urgency:** make (transition to) data-driven personalised care a national priority and further increase sense of urgency by creating sufficient support in the field and among the general public.

  This means increasing insight into the problem, increasing insight into possible solutions, inspiring action by showing what it can produce (getting things moving), and continuing to nurture support during this process (keeping things moving and anchoring).

- **Plan:** make use of already existing plans, such as those of VNO-NCW and MKB-NL

  The plans of VNO-NCW and MKB-NL are described in the reports 'vital people, smart care' and 'ahead with care: better, smarter, and more humane', but a strong party (the government) is needed, which takes the lead in creating support and involvement and in carrying out these plans.

- **Resources:** ensure sufficient resources (money, time, expertise). In order to apply PHC on a large scale, large investments are needed (e.g. from the private-public investment fund proposed by the entrepreneurial organisations) and existing resources need to be freed up where possible (e.g. by 'de-allocating' within the entire health care domain, radically scrapping senseless care and stimulating healthy behaviour).

- **Competences:** provide education and training and good public information

  Education and training of current and future care workers and good public campaigns[viii] are important to initiate the necessary changes.

3.2.5.3 Preconditions PHC: Building blocks 5 - 7

Building block 5: Access to meaningful 360° data

Barrier: **Limited access to meaningful 360° degree data**

Data coming from different sources ('data sharing') or rather the ability to analyse high quality training datasets to train an AI model, is a prerequisite for realising PHC: 'data is the fuel for the AI engine'.

- **Lack of good quality data:** data must comply with FAIR and FACT data[ix] principles to be able to shape and steer the rapid developments in the field of PHC. Not yet clear exactly which data should be collected (relevance). Actualisation of existing data is labour-intensive.

FAIR data
To make use of integrated datasets, we need to continuously validate the accuracy, reliability and veracity of data with new forms of big data analysis. It is therefore important that relevant data is findable, accessible, interoperable, and reusable: Findable, Accessible, Interoperable, Re-usable (FAIR).

FACT algorithms
Closely related to FAIR data is the social need for FACT data science. Only if big data applications and algorithms take into account important human values can they contribute to a better society for all. So it is important that algorithms are fair, accurate, confidential, and transparent: Fair, Accurate, Confidential, Transparent (FACT).

- **Data sharing is limited:** resulting in a lack of access to meaningful data in large quantities (Meaningful Data At Scale = MDAS):
  - **Prior consent required:** citizens/patients must give prior consent for the use of their data and for the specific purpose for which it is used. Secondary use of data requires a new consent.
  - **Conflicting business models:** lack of willingness to share data. Data is the gold of the 21st century. Data represents value for institutions (publications) and companies (innovations) and is therefore not easily shared (silos or scattered stand-alone databases). An example of how we took on the challenge of data sharing is the Immune Pro Hackaton.
- **Lack of interoperable (inter)national data infrastructure:** there is a lack of a technical infrastructure that makes sharing data and knowledge possible and easy;

For the Dutch situation, ICT is a major bottleneck[x]
Whereas decades ago, the Dutch healthcare sector was still at the forefront of ICT solutions, it is now lagging far behind. Databases are not equipped for new forms of data collection, for example by wearables, and the systems of GPs, pharmacists and hospitals communicate poorly with each other. With regard to the latter, the National Switch Point (LSP) only very partially meets the needs. According to professionals, the data in the LSP is not structurally maintained and is therefore far from accurate. Essential information is lost in a large amount of non-information or outdated information, which can have a major impact on patient treatment. Experts indicate that more attention is needed for ICT at both the national and international level in order to make optimal use of data.

- **No EPD:** the electronic patient file has not taken off in the Netherlands.

Direction of solution building block 5: **Improve quality of data collection, promote data sharing (adapt or replace informed consent model), invest in an interoperable (inter) national infrastructure, invest in creating an online personal health environment**

- **Improve the quality of data collection:** make existing data FAIR, develop standards for collecting data that may be relevant to PHC.

- **Promote data sharing:** Data is the raw material of the 21st century. Data sharing offers great social and economic opportunities. Promote access to relevant data, including future data (-omics) by promoting data sharing: collaborate on the data (Big Data) and compete on the analysis (AI).

  The Dutch government has expressed the ambition for Dutch companies to lead the way in promising and responsible data sharing. The following principles apply: data sharing should preferably be voluntary; if necessary, data sharing should be compulsory (as recently happened at European level with the PSD2 in the financial sector); people and businesses should keep a grip on data. The government puts this vision into practice: by encouraging ministries to put these data-sharing principles into practice in their domains; through research, cooperation and the exchange of knowledge; by promoting the Dutch data-sharing principles in Europe[xi].

Data donor code card
Introduction of a national or European data donor code card with which citizens/patients can voluntarily donate data to the government and/or industry in an AVG-proof manner, or anonymously if desired, in order to accumulate data to create valuable national and European data chains, from which new insights into disease and health can be distilled using AI. This can be seen as a modern version of 'making your body available to science'. The advantage is that while you are still alive, you can still witness the new scientific insights that emerge from this. A data donor codicil could be realised by amending the Donor Act. This concerns an active donor registration, which means that if people do not record their choice, they will be registered in the donor register with 'no objection' to donation. The observations and findings we make as citizens and patients are not only important for ourselves, but also for our health care system and our society. This is why we are allowed to ask citizens to do this. You can always say no (just like with the AH bonus card). Only together can we make healthcare sustainable.

Dynamic consent[xii]

Traditional research involves a pre-formulated hypothesis that is tested in the research. Modern PHC research makes use of 'data mining': data delving, in which one searches specifically for (statistical) links between different data sets with the aim of generating new hypotheses; identifying the combination of factors that may play a role in disease and health. These hypotheses are then discussed with experts, and promising hypotheses are tested in targeted studies.

PHC therefore requires permission to use data for a broad spectrum of different, possibly unknown future research activities. In addition, much of the data now stored in biobanks and databases was collected at a time when PHC was unthinkable. Thus, there are legal and ethical problems with secondary use of these data for PHC, because the patient has not given consent.

Dynamic consent is a method of information whereby patients, donors and/or participants in scientific research can give their consent for the use of their data and/or body material at several moments. Patients, donors and participants can give permission for new (sub)projects and can change their preferences over time. This makes it dynamic. Often a digital portal is used where consent is given electronically.

PSD2 paves the way for innovation[xiii]

In 2007, the Payment Service Directive (PSD) was introduced at European level. The PSD primarily served to unify the payment market within the EU. The directive has since been revised (PSD2). PSD2 facilitates all kinds of innovative payment services. With the introduction of PSD2, it will become possible for account holders to allow third parties to view their bank details. This third party can use these data to offer all kinds of services, such as payment services, but also financial technology ('fintech') options. Parties such as Apple, Google, Amazon or Facebook, for example, will soon be able to offer their own payment services that are linked to the customer's current account or credit card. PSD2 breaks the banks' monopoly on account data; now various (fintech) companies can offer all kinds of services that require access to account data.
The rationale behind PSD2 can best be summarised as 'working together on the data and competing on the solution or analysis'. Perhaps - by analogy - the introduction of an HSD2 (Health Service Directive) would be a good way to let the data flow better and thus accelerate the transition to PHC?

Data Sharing Platform (DSP) for PHC[xiv]

Data sharing is the ultimate prerequisite for unlocking the potential of PHC. Without data sharing, there will be no PHC.

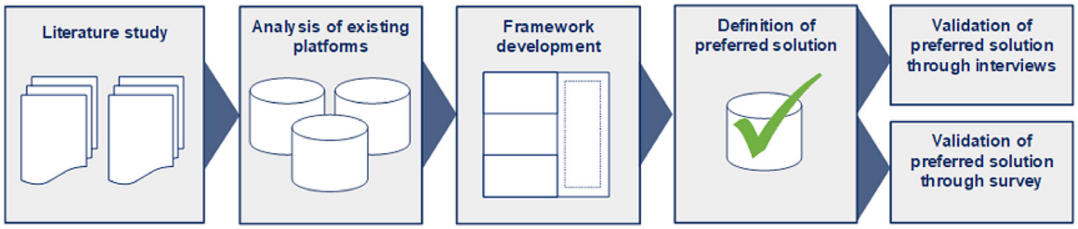
Data sharing is hampered by several issues:

- **Legal:** data sharing requires a solid legal basis: a DSP must act within the law and regulations. Current legislation on data sharing is vague, incomplete and lags behind, making it unclear what is and is not possible in the area of data sharing;
- **Cultural: data sharing requires a mindset of trust:** many companies do not yet have a clear understanding of what their data could mean for the company as a whole, and what other companies could do with their data. This lack of clarity leads to a lack of mutual trust and a reluctance to share data outside their own organisation. Public opinion on data sharing does not help either (data leaks, distrust of large companies with commercial interests);
- **Technical:** data is not stored homogeneously or in the right format. And data security is also an issue, because medical data contains sensitive information;
- **Value:** there is no generally accepted method for determining the value of data.

A DSP could play a role in breaking down these barriers:

- **Legal:** to be developed by DSP in close cooperation with VWS, Patiënten-federatie, Autoriteit Persoonsgegevens;
- **Cultural:** through clear contracts describing why data is shared and what happens to it, as well as what happens to any resulting IP; through working together towards a common goal; through better understanding of the full range of use cases of a given dataset;
- **Technical:** a DSP forces you to deliver the data FAIR;
- **Value:** there is no standard yet for valuing data. This should be possible by using foundational and financial measures (intrinsic, business, and performance value or market, income, and cost value respectively).

The PHC Catalyst Alliance, in collaboration with PNA Group, conducted a study ('Sharing is Caring') to develop a DSP solution framework and then select a preferred solution:



DSP Design: Summary

Prerequisites

Ownership of data	ownership of the source data always stays with the original owner, unless the ownership of the original is transferred to a different owner.
Permission to the platform	an invite-only platform.
Access to metadata	open sharing of metadata among platform users.

Platform parameters		Platform styles		
Data storage	A centralized data store containing both unstructured and structured private data vaults	OP	MP	CP
Standardization	A glossary with clear and specific descriptions for the variables. Strictly PHC related data.	OP	MP	CP
Data governance	Access to the platform granted through invitation, access to data granted by data providers. Governance of the standard by either a platform member or third-party.	OP	MP	CP
Data permission	Access to and use of data granted on a per-project basis.	OP	MP	CP
Data distribution	Access to data through a server with limited connections.	OP	MP	CP
Resulting IP	IP ownership should be determined by the involved members and included in the data sharing request (and data sharing agreement).	OP	MP	CP

OP = open platform, MP = marketplace, CP = collaborative platform

For more information, read the study report 'Sharing is Caring' on our website: https://www.phc-catalyst.nl/

- **Invest in an interoperable (inter)national data infrastructure:** Setting up large-scale data infrastructures for PHC is complex and requires the efforts of many parties and disciplines (e.g. HEALTH-RI: but their focus is on research and not on implementation). But it would also be easy to make use of the possibilities that already exist by linking existing databases (e.g. PHARMO, CBS).

  PHC is the future for healthcare, healthcare is a key driver of our economy, and in the digital world healthcare does not stop at national borders. Other countries are much further ahead. Hence our call: make (the transition to) data-driven personalised care a national priority, and make the best possible use of what we already have.

The power of a unified data infrastructure: COVID-19 and beyond[xv]

The COVID-19 pandemic has shown us how important it is to tailor healthcare to the individual, as clinicians need to understand the interplay between the many manifestations of coronavirus infection and the underlying biological processes of the individual.

Dr Ron Herings, Director of the PHARMO Institute for Drug Outcomes Research, and Professor of Pharmaco-epidemiology and Healthcare Optimisation (Amsterdam UMC), has developed a COVID algorithm that can predict which people are at greatest risk of serious disease following infection with the coronavirus. His research has shown that if you were to vaccinate these people as a priority, a 50% reduction in hospital admissions and mortality could be achieved with an 8% vaccination rate (1 million vaccinations). Without an algorithm, this result can only be achieved with a vaccination coverage of 50% (8.5 million vaccinations) or with a vaccination coverage of 24% (4 million vaccinations) if you were to vaccinate all Dutch people over the age of 60.

For the development of the algorithm, the existing PHARMO data infrastructure (linked databases) and the PHARMO network were used, whereby 500 general practitioners were prepared to fill in questionnaires regarding their sick corona patients. These doctors provide the necessary data, and the algorithm helps them to identify the patients who are most at risk. It is a contractual exchange of data and knowledge. The algorithm is now being extensively tested in North Holland and Flevoland. Ideally, this solution will be scaled up to 8,000 GPs.

This experience has convinced Dr Herings even more of the importance of developing a uniform infrastructure for health data: "On a technical level, we are actually already there. It is a Lego system. All the parts are there. Nothing needs to be invented. What COVID-19 has taught us is that we need the system now, whether it is for COVID-20, Q-fever, Epstein-Barr virus or anything else. And by keeping it organised by region, we keep the data safe in terms of privacy. You don't have to start all over again and invent a new system. But just use our data infrastructure and network approach. Just ask. And don't forget to give something back to those who provide the data. The Scandinavian countries use their health data in a meaningful way. The UK also has much better data access thanks to the NHS. I think it can be done in the Netherlands too. COVID-19 is just one example. The potential benefits of meaningful use of data are much greater. For example, we can use the data to personalise healthcare".

Dr Herings sees Amsterdam as a great place to start. "First Amsterdam, then the world. As I said, it can be incredibly frustrating if you have to build from scratch. So you really need support from the people in charge, the ones who dare and can make decisions, who unite different interests".

- **Commit to the creation of an online personal health environment:** in the Netherlands, MedMij is committed to the creation of an online personal health environment, in which every citizen can retrieve their own data from various sources, manage it and release it for research purposes.

Building block 6. Attractive earnings model

Barrier: Lack of attractive revenue model where the investor also gets the benefits

- **Lack of method to determine the economic value of data:** there is value in data, and this is an important reason why data is not (easily) shared. There is no method to determine the economic value of data, and no clarity on 'paying for data to promote data sharing' or 'paying by sharing'.

- **Lack of an attractive earnings model where the investor also gets the benefits:** The investor (financial or in data) is not the party who immediately experiences the benefits of PHC. In order to get these investors on board, a different revenue model is needed.

  The transition to PHC has the potential to create great value for Dutch citizens: we can gain healthy life years at lower costs. This shift is driven by existing and new players in healthcare. In exchange for the value they create for Dutch citizens, there should also be value for them to share. Yet the reality of value distribution in practice proves to be stubborn.

Solution direction building block 6: Develop new business models and a method to determine the economic value of data

- **Develop new business models.** Only by taking the perspective of all stakeholders into account, you can arrive at an attractive earnings model that is also feasible for all stakeholders (see Appendix 8). Value distribution is achieved by introducing (and seeking) the right incentives in the system and forming effective coalitions with the right balance between scale and complexity.

- **Develop a method to determine the economic value of data**[xvi]. Data is the raw material for new earning models: 'data is the gold of the 21st century'. Commissioned by the Ministry of Economic Affairs, the CBS has conducted and published a pilot study that describes a method for calculating the value of data and makes an initial estimate of the value of data. So this might be a start towards a future standard?

New money flows and revenue models: more focused on stimulating population health. The money flows in this new health ecosystem must also change. Reimbursement in silos, such as for primary care, hospitals and long-term care separately, does not fit with an integral management of patient health. A 'fee for service' reimbursement for treatment does not fit a world of data-driven prevention.

New money flows will also lead to new revenue models for the traditional and the new players within the health ecosystem:

- For the traditional players, value creation is sometimes an elusive phenomenon. Initiatives that work well locally are often not sufficiently scaled up. Initiatives that start on a larger scale often get stuck in too much complexity. Besides the challenges of scale versus complexity, these parties also face the wrong incentives in our system. The party that has a crucial role in creating added value sometimes loses out in our system.
- For new players in healthcare, our current healthcare ecosystem can seem like a complicated labyrinth. A place with many stakeholders, vested interests and an incomplete market. These companies come from market ecosystems where "value creation for an end customer" leads to "Return on Investment" in the form of a larger share of the "profit pool". For them, healthcare often seems to be a place where a different language is spoken and a different logic applies.

What can individual health ecosystem actors already do to promote innovation and value creation in the health system?

This article outlines a concrete step-by-step plan that can already be applied to forming an ecosystem coalition around innovations in Dutch healthcare.

Step 1: Define the target group and quantify the value you bring to them

Step 2: Determine who is paying and what they are willing to pay for this improvement

Step 3: Determine the expected return on investment

Step 4: Determine the ecosystem coalition, and how there can be a 'net positive value' for each party

Step 5: Set up the coalition with an explicit shared vision of value creation and value distribution

Building block 7. Required working frameworks and agreements

Barrier: Lack of PHC policies, related laws and regulations, and standards and shared language

- **Lack of PHC policy:** the unfamiliarity with PHC, also in the government, results in the lack of a clear PHC policy to enable the transition towards PHC.

- **Lack of related laws and regulations:** lack and misinterpretation of laws and regulations, lack of clarity on the coherence of laws and regulations, insufficient use of free space, and a vacuum during the period when new laws and regulations are being developed.

1. There is a lack of laws and regulations and they are often misinterpreted;

General Data Protection Regulation (AVG)[xvii]
The AVG, the privacy legislation that gives citizens control over their own data, can be interpreted in different ways. The AVG is experienced by some companies and institutions as a burden and an obstacle, but they can also benefit from it:

- **Benefits:** By dealing responsibly with privacy, an organisation can win the loyalty of people, because they trust the organisation. In the long run, it can even be very useful for organisations, because working in compliance with the AVG creates a data structure that can lead to more productivity. In addition, organisations can now have more accurate data, as people can access their data, check it and indicate whether the data the organisation has is correct.

- **Cons:** With the AVG, organisations are responsible for the personal data of their customers. Data leaks can occur and an organisation can be hacked. Organisations must be able to demonstrate that they handle this data properly, otherwise they risk an enormous fine. Misunderstandings about the protection of personal data can also arise. For example, organisations may think that encrypting personal data is sufficient to protect these data, but organisations must do more to protect data. In addition, organisations can shift the responsibility to cloud providers, if they store their data in the cloud. Cloud providers are also responsible, but so are the organisations that collect this data. This was initially unclear to organisations.

2. There is a lack of clarity about the consistency of various laws and regulations that should apply to PHC;

Consent to the sharing of medical data between healthcare providers[xviii]
When consent is needed for the exchange of patient data and when it is not, differs. The rules that apply are, in fact, laid down in various laws. Where the exchange of patient data between healthcare providers is concerned, this is mainly regulated in the General Data Protection Regulation (AVG), the AVG Implementation Act (U)AVG), the Medical Treatment Agreement Act (WGBO), and in the Act on Additional Provisions for Processing Personal Data in Healthcare (Wabvpz).

The main rule
The main rule is that **explicit** consent must be given.

When is explicit consent legally valid?
Consent must meet the following requirements: **freely given, unambiguous** (there must be an active action, for example a (digital) written or oral statement) **informed** (the patient must know the purpose for which the data is requested and/or provided, which data, must be able to understand the scope of his consent, must be informed about his right to withdraw consent), **specific** (consent must always apply to a specific processing and a specific purpose; consent must be requested separately for each purpose).

From whom must express consent be obtained?
Younger than 12 years: **legal representatives**, 12-16 years: **together** (if capable of reasonable evaluation of his interests), 16 years and over: **alone** (if capable of will).

Exceptions which do not require the patient's explicit consent
Statutory duty or task, **vital interest** (the patient is unable to give consent), **exceptions** (directly involved in the treatment, exchange with substitute or deputy), **presumed consent** (referral by the patient, informing GP by healthcare provider), **conflict of duties** (emergency situation).

3. The free space is used too little. Within the legislation and regulations (AVG) there is room that is currently insufficiently used. People are afraid to commit an offence and sticking your neck out is rarely rewarded. This spasmodic clinging to a too strict interpretation of legislation and regulations starts at the government level.

4. A vacuum is created in the period when new laws/rules are developed, accepted/adopted and implemented. So, although it may already be clear that something will or will not be allowed in the future, other rules apply at the moment. Especially when developments are rapid, related laws and regulations will always lag behind, sometimes even by years.

- **Lack of standards:** lack of standards and shared language

  – Lach of standards: PHC is still under development. There is a need for standards in all steps of the implementation, agreed with all stakeholders, so that everyone knows what to expect from each other.

– Lack of shared language: The lack of an unambiguous understanding of PHC. There is no generally accepted definition of PHC (yet), so that different meanings are given to the concept of PHC. Where PHC stands for personalised healthcare based on individual characteristics (data-driven healthcare), some mistakenly assume that PHC stands for a personal approach (tailored to the wishes, needs and expectations of the patient: 'patient-centred') and dismiss PHC as 'we already do that, patient-centred'.

Solution building block 7: **Develop necessary PHC policies, related laws and regulations, and standards and shared language. See in this context Appendix 6.**

- Also look at what is happening in other European countries, such as Estonia and Finland. What is possible there, must also be possible in the Netherlands. See in this context also **Appendix 6**.

Secondary Use of Data Act (Finland)[xix]
In Finland, the Social Insurance Bank has built a national Electronic Patient Record (EPD) for 5.5 million Finns. In total, there are about 2.3 million users.

- The Finnish government - in full compliance with the European AVG directive - has made a law on secondary use of medical data, which can then be used by companies and researchers;
- Because Finns now have access to their medical records, doctors have started to take clearer notes because they were asked many questions;
- In the Finnish EPD, it has been made possible - after permission - for a private app to have direct access to the medical file. In this way, an employer's digital vitality platform can offer smart health services, taking into account the worker's medical file.

What is interesting about the Finnish system is: a centralised database (at low cost), a direct link to the private consumer market and the possibility of using the data for services and research. It is precisely the availability of data for improving preventive healthcare that can enable companies to develop useful and new applications using the available data. In the Finnish system, all this is accompanied by public safeguards and regulations. Finland is a member of the EU, so everything complies with European laws and regulations.

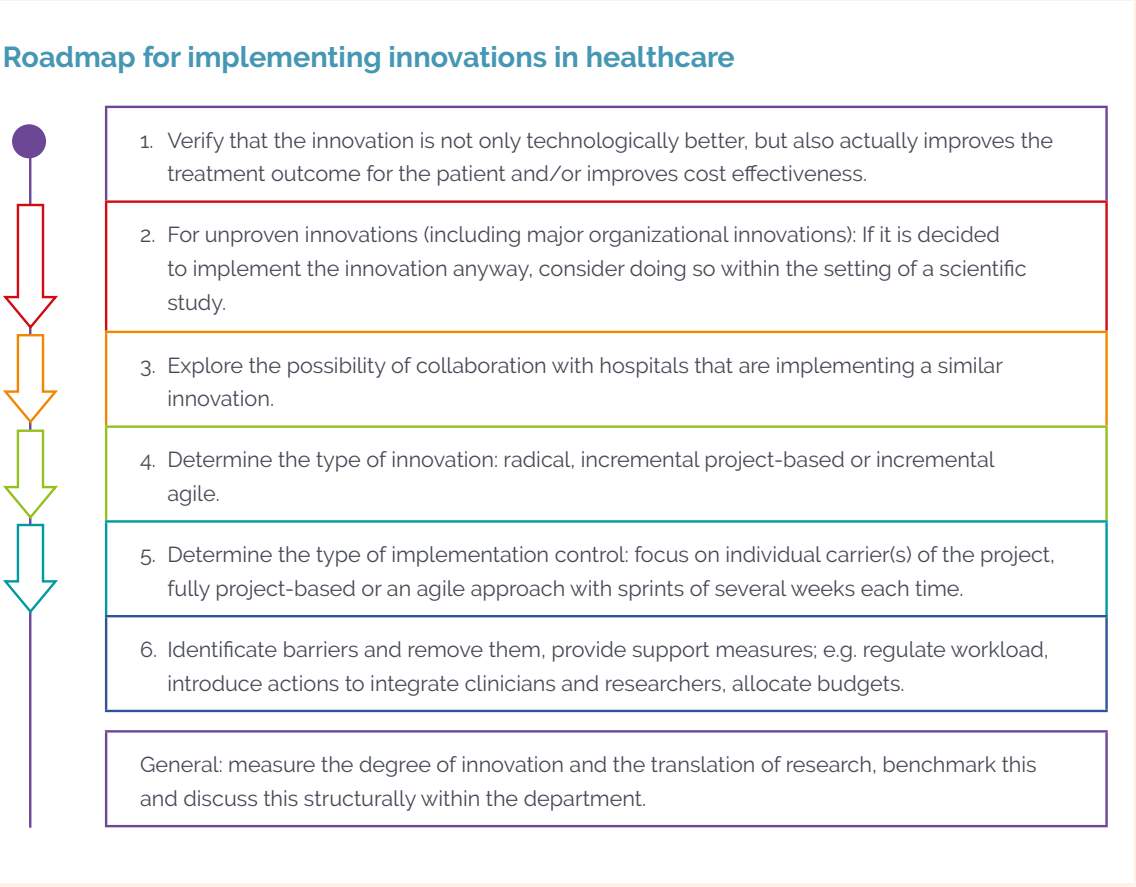
Standards to be developed

Standards for collection of genetic information and other data that may be relevant to PHC and AI: clinical sampling, analytical tests, data analysis, data interpretation, data storage, data exchange, data visualisation for use by practitioners and patients.

Standards of evidence for registration, reimbursement and inclusion in guidelines of PHC solutions: what are the assessment criteria?

Standards for implementation in daily practice: The literature shows that there is no single best way to implement, as this depends on many environmental factors. However, there are a number of general principles that always apply. In the figure below, these steps are described, which are obvious to implement more effectively and efficiently in radiotherapy, and, although not studied, probably also in other fields .

Figure 5: Roadmap for implementing innovations in healthcare (source: Jacobs et al, 2018)



3.2.5.4 Proof-of-Concept: Building block 8

Building block 8: Proven cost-effectiveness and clinical benefit

Barrier: **Difficult evidence PHC: 'application and evidence hold each other hostage, as it were'.**

- **Cost-effectiveness:** unclear what type of evidence is needed to demonstrate the (cost) effectiveness of PHC applications.

  Everyone is waiting for proof, but this proof will not come without application
  PHC aims to treat patients based on their unique characteristics. The scientific knowledge on PHC is in full development. It is becoming increasingly clear that many factors combine to determine whether a person responds well to treatment, but there is still much unknown about the influence of all these factors and their interaction on the expected therapeutic outcome. These gaps impede market acceptance, while much can be learned from practical application: feedback of treatment results (for whom does it work? for whom does it not work?) can provide new insights (which as yet unknown factors may play a role?) that make further personalisation possible. There is a self-reinforcing mechanism: the more we apply, **the more we can learn**.

  However, everyone is waiting for evidence that, according to the *current standards*, has sufficient probative value for market approval (RCT), but the provision of this type of evidence is hampered by the relatively small patient groups (RCTs not possible): **application and evidence are, as it were, hostage to each other.**
  This problem with evidence also applies to conditions that are (very) rare, and for these the Minister has decided to grant conditional admission to the basic health insurance package before sufficient clinical evidence has been collected to demonstrate the effectiveness of the medicine. This faster, but conditional, admission applies to all patients, and the Care Institute provides scope for demonstrating the effectiveness of the medicine in practice. In addition, drug companies must commit to a reduced price during the conditional authorisation period. This also seems to be the appropriate route for PHC.

- **Clinical benefit:** innovations often fail to cross this threshold from research to practice (insufficient evidence of clinical benefit). This gap between science and practice is caused by the lack of innovation implementation research (from research to practice) and feedback of practice results (from practice to research). For evidence at the level of clinical benefit, not only the quality of the innovation should be clear, but also the context in which the innovation could be applied.

  In Maastro, the percentage of publications, which has been implemented in clinical practice ('the leak in the research innovation pipeline'), was investigated. In 2015, this percentage was 19%. Since then, the focus has been on translation and the percentage has risen to 25% in 2019.

Pharmacogenetics test
There is a discrepancy between the evidence needed to consider a pharmacogenetics test useful and the evidence provided by scientific research. The evidence available from clinical trials is of low strength. On the one hand, this is because patients are divided into subgroups that are too small to generate sufficient statistical power. On the other hand, few prospective studies are undertaken. In addition, pharmacogenetics does not always help in choosing the right treatment, due to insufficient evidence of a direct link between pharmacogenetics and improved clinical outcomes (not every condition can be easily genotyped). The outcomes can also be ambivalent, for example side effects are experienced differently by different patients. Furthermore, genes are not the only factor influencing the (undesirable) effect of drugs. Diet, lifestyle and the functioning of organs, such as kidneys and liver, also have an influence. Also, there are not always alternatives if genetic testing shows that the patient may not benefit from the drug or may experience side effects. If these obstacles do not exist, pharmacogenetics can be successfully used to prevent ineffective or even harmful pharmacotherapy. A point for attention remains, however, the measurement of relevant parameters that are necessary for the translation of scientific evidence into clinical practice. For example, there is a need among healthcare providers for evidence at the level of clinical usefulness, whereby attention is also given to the context in which the test could be applied. Not only should the test properties be clear, such as the predictive values, but also the target population. Characteristics of the target population are important, such as the frequency of side effects, but also the responsibilities of the healthcare providers involved.

Solution building block 8: **Further refine current PHC knowledge, close the gap between science and practice, create space for alternatives to build evidence in practice.**

- **Further refine current PHC knowledge:** identify missing factors and interactions that play a role in disease complexity.
- **Closing the gap between science and practice:** Intertwine research and practice more closely. Ensure that research results can be used more quickly in practice and that data from clinical practice can be used more easily for research. For funding implementation research, bring together sources from government, health insurers and pharmaceutical companies.
- **Create space for alternatives to build evidence in practice:** consensus needed on data collection in practice: 'instead of n-of-1 trials are relevant when Randomized Clinical Trials (RCTs) are not applicable or available, how about RCTs are relevant when n-of-1 trials are not applicable or available'.
- **Diverge and converge:** In the current system, treatment must first be shown to be useful before it can be applied in daily practice. Whereas in the case of tailor-made treatment, we could *learn* a lot *from an initial broad application* in daily practice to be able to better predict in the future for which profiles/subtypes treatment is useful. So, first diverge and then converge.

3.2.5.5 Proof-of-Business: Building block 9 - 10

Building block 9: Registration, costing and reimbursement, inclusion in directive

Barrier: **PHC applications are mostly not reimbursed and little is included in the guidelines**

Lack of clarity regarding registration, funding and reimbursement, and inclusion of PHC applications in guidelines exists: PHC diagnostics and PHC treatments are often not reimbursed, and there is little mention of PHC in guidelines.

- **PHC is still a relatively unknown area for the government and the field.** They view PHC through the lenses of the current system ('old thinking'). But PHC is difficult to fit into a system in which EBM and large RCTs are decisive for registration, reimbursement and professional guidelines. After all, large RCTs cannot be conducted with small patient populations. It will therefore be necessary to rely much more on data collected in daily medical practice (RWD).

- **The quality assurance agency has yet to develop the market approval criteria for PHC.** The result is a lack of clarity regarding the registration, reimbursement and inclusion in guidelines of PHC applications. In addition, there is increasing social pressure for early and rapid access to innovative medicines. The sustainability of the market authorisation system is under discussion.

Course of action: **Adapt/eliminate market admission criteria to the new reality of data-driven personalised care, create financial space for funding and reimbursement of PHC solutions, encourage inclusion in guideline.**

- **Adapt/eliminate market acceptance criteria to the new reality of data-driven personalised care:** Create a flexible/dynamic system instead of a rigid/ static system. This means, for example, for registration 'rolling review' (as with the Oxford corona vaccine) for access and payment, where we collect additional data on effect and side effects, and reduced price during this conditional approval period (by analogy with rare diseases). A shift towards early access and outcome-based payment schemes.

- **Create financial room for funding and reimbursement of PHC applications:** To make room for PHC, in addition to a new view of health (shift from sickcare to healthcare), a new view of healthcare is needed (**see Appendix 2**). For example, you will have to start as soon as possible by radically scrapping senseless care and (financially) promoting healthy behaviour.

- **Encourage inclusion in guidelines, ensure quick implementation of guidelines:** optimise the input of PHC experts in working groups that draft guidelines, make guidelines a joint responsibility (multi-stakeholder guideline) and each of these parties can put the updating of the guideline on the agenda.

Building block 10: Dissemination, adoption, implementation, assurance[4]

Barrier: Lack of awareness of PHC among patients and the general public, limited knowledge among medical physicians about possibilities and applications, limited experiences and convictions on the part of physicians, other other obstacles to the application of PHC ('unknown makes unloved')

Solutions building block 10: Take your time, create narrow but deep support, build a lobby for PHC, create room for experimentation, create a safe environment for people, reduce obstacles to PHC implementation

- **Take your time:** to come to deeper forms of understanding.
- **Create narrow but deep support:** you have to learn to play chess. Place every action you take in a wider perspective (yourself, your organisation, your environment).
- **Build a lobby for PHC:** use frontrunners, use successful examples, ensure adjustments in the curricula of medical-technical training, good public campaign, use various communication means and channels.

Education

The PHC Catalyst Alliance has conducted research on education. There is a lack of adequate education. There is still a world to be won here. Most courses only touch upon one or sporadically a few knowledge domains relevant to PHC, but an integral PHC viewpoint is lacking. Many courses are for a specialised audience, making them inaccessible to most PHC practitioners. University courses are scarce, only 3 courses are specifically dedicated to PHC. PHC is alive and well in Germany, especially in university hospitals. A few universities have courses on PHC, like the Technical University of Munich. We see that the German government takes an active stance towards PHC. The Ministry of Education and Research invests in activities and initiatives to cooperate in the field of PHC.

The core domains for PHC are: (1) systems biology and systems medicine, (2) advanced diagnostics (a.o. genetics, -omics, microbiome), (3) medical imaging, (4) personalised treatments, (5) data science & bioinformatics (6) legal and ethical.

The table below shows per stakeholder group the desired knowledge level for the different core domains:

[4] Dissemination = people involved are informed about the change; Adoption = people involved are positive about the change; Implementation = people involved learn to deal with the change and actually carry it out; Safeguarding = people involved have integrated the change into their professional actions, into the functioning of the organisation, or into the structure of the sector.

knowledge domain / stakeholder group	-omics	Systems biology	Personalized medicinal products	Genetic engineering	The human microbiome	Biomarkers	Medical imaging	data sourcing	data wrangling	data analysis	model interpretation & evaluation	model visualisation	results interpretation & evaluation	results visualisation	Legal	Ethics
caretakers	1	2	1	1	1	1	2	1	1	1	1	1	2	2	2	2
citizens	1	2	2	2	1	1	2	1	1	1	1	1	2	2	2	2
education providers	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
general practitioners	3	4	3	3	4	4	2	4	1	1	1	1	3	3	3	3
government	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4
health insurers	2	2	2	2	2	2	2	4	1	1	1	1	3	3	4	4
IT service providers	2	3	2	1	1	3	2	5	5	5	5	5	5	5	3	3
laboratory workers	3	3	3	3	2	3	4	5	2	2	2	2	3	3	3	3
medical specialists	3	3	2	2	1	3	2	2	2	2	1	1	4	4	3	3
nursing staff	2	2	2	2	3	3	4	2	1	1	1	1	4	4	2	3
paramedical specialists	2	2	1	1	1	2	2	1	1	1	1	1	2	2	2	2
patients	1	1	2	2	2	2	2	1	1	1	1	1	3	3	3	3
pharmacists	3	3	4	2	2	2	2	3	1	1	1	1	2	2	3	3
producers	1	2	2	1	1	1	2	3	2	2	2	2	3	3	4	4
regulators	3	3	2	4	2	2	2	2	2	2	2	2	4	4	5	4
scientists	5	5	5	5	4	4	3	5	5	4	5	5	5	5	3	3
service providers	1	1	2	2	2	2	2	3	2	2	2	2	3	3	3	3

Level	Type	Description
1	Novice	Barely aware or not aware of the knowledge and how it can be used.
2	Beginner	Knows that the knowledge exists and where to get it but cannot reason with it.
3	Competent	Knows about the knowledge, can use and reason with the knowledge given external knowledge bases such as documents and people to help.
4	Expert	Knows the knowledge, holds the knowledge in memory, understands where it applies, reasons with it without any outside help.
5	Master	Internalizes the knowledge fully, has a deep understanding with full integration into values, judgments, and consequences of using that knowledge.

For more information, please read the study report '[Sharing is Caring]' on our website: [https://www.phc-catalyst.nl]

- **Create room for experimentation:** to let people experience the benefits of PHC.
- **Create a safe environment for people.**
- **Reduce obstacles to PHC implementation.**

Finally

Led by the Netherlands Healthcare Institute and the Dutch Healthcare Authority, the 'Digital Healthcare Sandbox' was introduced, inspired by the financial sandbox as it exists in the Netherlands and is organised by the regulators (DNB, AFM).

The ZorgZandBak invites parties who are stuck in their 'Last Mile', particularly where this is caused by (interpretation and/or amendment of) legislation and regulations.

The Digital Care Sandbox[xxi]

The Digital Care Sandbox was created as a result of the fact that innovation and transformation in the care sector encounter barriers for various reasons, while the (digital) innovation or change has demonstrable added value for patients and care providers. For example, the innovation or change leads to added value for the patient and his or her perceived quality of care, contributes to a reduction in healthcare costs or a more efficient use of scarce resources, contributes to health in a broad sense and improves the experience of the healthcare provider, but still runs up against issues of quality, costing, accessibility and/or legitimacy. These are usually not easy issues to solve.

Solving these kinds of 'exemplary' issues requires a more open approach, one that allows for experimentation and learning together to achieve successful innovation and transformation. For the approach, we looked for inspiration in sectors that are also dealing with similar issues. This is how we came up with the sandbox innovation method. This method offers room to work together, to investigate, to develop and to come to decisions. It is an environment in which solutions are sought transparently, but also in which clarity is provided about what is and is not possible.

3.2.6 Literature review

The findings (building blocks, barriers, possible solutions) of our study are supported by literature research[ix] (**see Appendix 6**). In the literature, the focus is on precision medicine (PM), because this narrower perspective of PHC is currently mainly applied in practice.

We also searched the literature for the main reasons why implementations fail in general (and then related this to PHC):

1. Complexity

The greater the complexity, the greater the chance of failure.

The complexity factor of the transition to PHC is high. PHC is complex (project: content, scale), the healthcare landscape is complex (organisation: many stakeholders), and the user groups are complex (citizens/patients: inhomogeneous groups). Care providers have to work with a new model (exploration: introducing innovations), but are also still in the middle of the old system (exploitation: producing). This new model (PHC) also requires far-reaching cooperation (combinatory innovation) and an entirely different approach (experimental learning). These are changes that are difficult to achieve in the current rigid healthcare system. There is much to be learned from system transitions in other countries and other sectors that are ahead of the Netherlands and the healthcare sector.

There is an additional complexity factor, namely the fact that PHC is still under development. This concerns not only advanced diagnostics and personalised treatments, but also the technologies and standards to store, analyse and model big data. But if we are unable to implement existing PHC innovations now, what about the tsunami of PHC innovations to come?

Solution: In order to accelerate the transition to PHC and to properly carry out the important implementation phase, it is necessary to map out all the perspectives of the parties that make up the complex healthcare system. The key questions are: 'how to maximize the common good' and 'how to resolve individual, conflicting interests'. Sometimes, compensation from the collective will be necessary to achieve an acceptable 'win-win'.
Furthermore, much can be learned from system transitions in other sectors (financial sector leads the way in digital transformation, healthcare sector lags behind) or other countries (UK, Scandinavia). Finally, 'Think big, start small, learn fast'. For example, start in '1 disease and roll it out to other hospitals' or start in '1 hospital and roll it out to other diseases'. In the latter case, think of LUMC, which has defined 'groundbreaking improvement' as its mission, whereby it is positioned as an innovator for the improvement of healthcare and human health and PHC is a strategic spearhead.

Nowadays, organisations must be able to function "in a balancing act[xvii]
On the one hand, operational activities must be carried out effectively and efficiently, while on the other hand, innovations must be conceived and introduced to secure the future. Operating effectively and efficiently is often associated with standardisation and the reduction of variation, while innovation goes hand in hand with increasing variation, research and experimentation. Thirty years ago, the literature already indicated that organisations must give balanced shape to these two things, also referred to as *exploitation and exploration*. For a long time, the two types of activities were seen as opposing constructs that should be organised at different locations in the organisation. Nowadays, however, the idea is that both types of activities can (should) take place at the same time in the same organisational unit, whereby it must be determined at the level of that unit how the conflicting activities can best be carried out, depending on the specific context at that moment (contextual ambidexterity).
In Maastro, we have introduced innovation teams. These appear to be teams separate from the daily clinic, but that is not really the case. The teams are largely made up of people who work regularly in the surgery. However, specific weeks have been planned during which these people from various disciplines (e.g. lab technicians, doctors, physics, IT) are not scheduled for regular work but, in a so-called sprint week, will work together in a multidisciplinary manner to achieve a predefined result. The innovation teams are led by programme managers who monitor the total implementation plan. This also ensures that sufficient resources are available for the relevant part of the innovation implementation process, as we know that this is an important success factor.
Within Maastro, we are going to investigate the added value of innovation teams. We also hope that this will provide a scientific basis for a good form of contextual ambidexterity, in which we can simultaneously manage our daily operations effectively and efficiently and innovate on a large scale.

2. Insufficient support and lack of clear objectives

Support is essential for implementing change.
In order to create support for the transition to PHC, it is important to draw attention to PHC, to emphasise its importance and urgency, and to clarify its ultimate goal. This requires a clearly formulated vision.

PHC Catalyst Alliance - vision: what are we aiming for?
In order to accelerate the transition to personalised care, the healthcare system must be designed and adapted in such a way that it stimulates personalised health and care rather than working against it or creating a receptive environment:

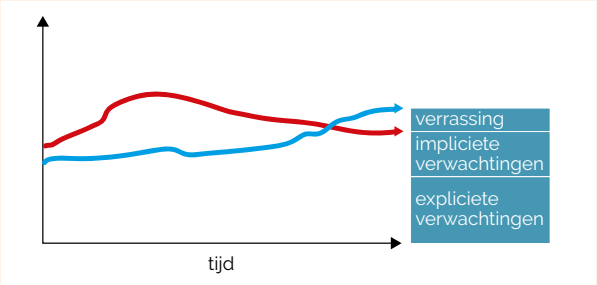
- **Innovations** are quickly and widely (nationally) implemented in daily practice (with a particular focus on the last part of the innovation process, the 'Last Mile', in which promising initiatives often encounter difficulties), which requires adjustments to legislation and regulations, research, registration, funding and reimbursement, and supervision;
- To increase **knowledge and skills in the areas** of systems biology and systems medicine, big data, advanced analytics and technology;
- **Diagnostics and treatment** are aimed at the right care in the right place for each individual patient. This means care that matches both the unique biological characteristics (genotype) and the unique needs of the patient (psychosocial factors: the patient's own living and thinking environment, as close to home as possible);
- **Care** is shifting from managing symptoms to treating the underlying cause and preventing diseases and complications;
- **Citizens/patients** are (continuously) provided with reliable information on their own health in order to be able to make informed choices;
- **Collected data and acquired knowledge** are shared (linking data and knowledge). Data at individual level contributes to the development of knowledge about disease and health at population level.

3. Expectations that do not come true due to "old thinking

If it is not the new opportunities, but the old thoughts and habits that are leading, the feeling can arise that the innovation is not what one had expected and hoped for.

Solution: be alert for 'old thinking' and spend time managing expectations

Managing expectations
Expectations management is "managing the difference between what someone hopes to get and what someone is going to get".



The expectations that someone has are not always clear beforehand. There are explicit expectations, i.e. that part of the delivery that is clearly described in the project plan. However, there are also always implicit expectations, i.e. all the things that the other party expects without these being put down on paper or even expressed. They are taken for granted by the other party, but perhaps not by you.

Meeting expectations: The most common way to do expectation management is to find out as much as possible about the implicit expectations. Next, you manage the project or your people in such a way that these implicit expectations are also met. That is not so easy, because just try to find them all out.
Managing differences: There is also another way to manage expectations. You can also manage what the other person expects to get. The definition above is about managing the difference. Of course you have to make sure that what you are going to deliver (the blue line) meets the expectation (the red line) as well as possible. But many people forget that you can also manage the difference by steering the expectation of the other person. This means that you continuously steer towards what the other person expects to get. Looking at the figure above: you are not only going to 'manage' the blue line upwards, but you are also going to 'manage' the red line downwards: in other words, '*underpromise and overdeliver*'.

4. People do not understand what implementation is or underestimate this process

Many people have the idea that an innovation is complete when the development of the innovation is finished.
There is little awareness and/or knowledge of social innovation: if you want to create value, then the implementation phase (from 'Proof-of-Concept' to 'Proof of Business') must also be done well and thoroughly. If you don't do this last mile, it will be difficult to make it a success.

***Solution:* define and plan the innovation implementation trajectory just as thoroughly as the development of the innovation. Be aware that such a trajectory is also customised.**

- Finally, we searched the literature for ways to increase the chances of implementation success:

  "Studies find many determinants of successful innovation implementation. There is so much literature and so many factors that are statistically significant, that the translation to practical knowledge when innovating in practice is sometimes difficult. Rachelle Swart, one of Maastro's PhD students, has developed a prediction model to calculate the chance of timely implementation of innovations before the project starts. Success is defined as the implementation of a project within six months of the planned end date. It turned out that there are only 5 factors that predict the chance of success. Two of these 5 factors are determinants that cannot be managed (well), namely the type of innovation and the complexity. The model has not yet been externally validated".

A prediction model for successful innovation implementation
Five factors that predict the likelihood of success:
- **Type of innovation:** treatment innovations are 4 times less likely to be successful than technological innovations. This is not yet well explained based on current literature and is being investigated further;
- **Complexity:** complexity is a function of variety (presence of many professional disciplines, many functionalities, and many project members). To compensate for complexity, you can, for example, hold interactive work sessions with the project participants to make everyone aware of the relevant aspects of the project;

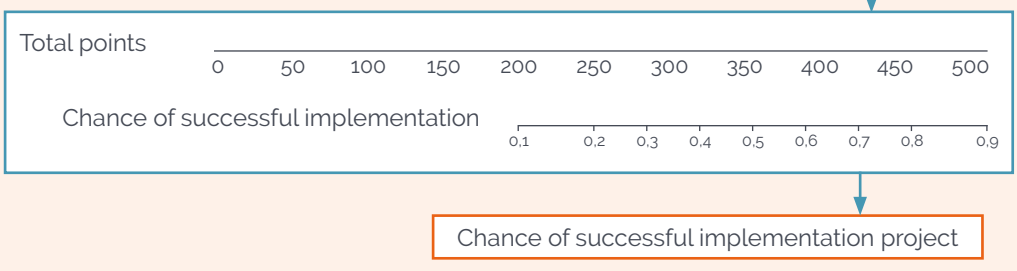
- **Sufficient and competent staff:** if you do not have this in order before starting a project, the chance of not implementing it or incurring a delay of more than six months is almost 6.5 times greater than if you have your resources in order;
- **All members of the project must be well aware of the project's goals and the process to be followed:** if this is made clear to everyone, the chance of success is five times higher than if it is not made clear enough or in sufficient depth;
- **Degree to which the project is desired and considered feasible:** here, too, the chance of success is five times higher than when there are doubts.

It seems useful for project members to score these success factors before the project starts. As there are few factors to be scored, this is not too time-consuming.

STANDARD OPERATING PROCEDURE (SOP): Preparation for start of project

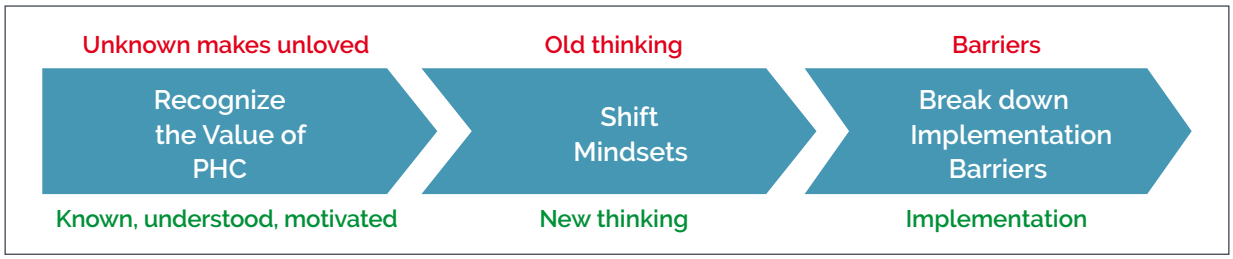
1 Make decision to introduce innovation.
2 Write project plan.
3 Predict the likelihood of successful innovation implementation. All project members score the project/innovation according to the questions and answers below. Then the nomogram is consulted to calculate the probability of successful innovation implementation.
4 Support decision making on whether or not to launch the project with the results of the Model: Projects with a certain percentage or higher can start. The lower limit should be determined by each organization, for example 70%. For projects that have less chance of a successful implementation than that lower limit, i.e. 70%, action must first be taken to increase the score on the success factors.

Success factors *Are the following factors present by the project?*	**Project Time X** *Yes* / *No*
Is the project an organizational innovation?	38 / 0*
Is the project a treatment innovation?	0 / 78*
Is there sufficient and competent staff to carry out the project?	100 / 0*
Are the goals of the project and the process communicated so well with team members that these are completely clear?	85 / 0*
Is the project/innovation considered feasible and desirable?	90 / 0*
Is it a complex project (integration of functionalities and devices/many professionals)	0 / 93*
Total points: **Average points project:**	X (sum of the total number of point) total number of project members



3.2.7 Conclusion

- The success and failure of the implementation of PHC is not only determined by the value of PHC, but also by various behavioural and environmental factors. There is work for all stakeholders in the healthcare field to promote the conditions for implementation in order to actually achieve scaling up.



- Smarter use of limited collective resources creates the financial space needed to invest in PHC and thus make healthcare more sustainable.

3.3 SWOT analysis for PHC

	Helpful to achieve objectives	**Harmful** to achieve objectives
Internal attributes	**Strengths** • Strengthens efficacy and efficiency of healthcare and reduces cost to society • Shift from managing symptoms towards treating the underlying cause and prevention	**Weaknesses** • Evidence that is needed to facilitate PHC: not only are disease mechanisms highly complex, individual parameters do not reflect the full story; • Technologies to store and analyse big data and to try to model them are not fully developed yet; • Changes in healthcare system will be hard to realize in the current rigid system
External attributes	**Opportunities** • The burden of chronic disease is on the rise • Healthcare policy makers and doctors are increasingly mandating what doctors can prescribe • Pay-for-performance is on the rise • The boundaries between different forms of healthcare is blurring (from doctor to ancillary care or self care; from hospital to primary care) • Many government begin to focus on prevention (health management) rather than treatment (sickcare) • Wealth of PHC solutions (Dx, Rx, CDS) in the pipeline	**Threats** • Complexity: multi-stakeholder involvement • Regulators are becoming more risk averse

4. Roadmap towards the PHC future

In order to accelerate the transition to PHC, we have drawn up a pragmatic step-by-step plan based on the change methodology of John Kotterii.

4.1 Urgency

Step 1: Create a sense of urgency: make (transition to) data-driven personalised care a national priority

*This is also the key message of the manifesto[xxii] of the PHC Catalyst Alliance (see **Appendix 7**), which can be signed on our website: https://www.phc-catalyst.nl/*

- Help others see why change is necessary, and why it is important to act immediately:
  - Healthcare costs are rising at an ever-increasing rate and are skyrocketing. This growth in healthcare costs is unsustainable and unmanageable in the long run;
  - PHC is the way to make healthcare sustainable: 'from unsustainable sickcare towards sustainable healthcare'.
  - PHC solutions are currently mainly experimented with and do not cross the threshold from research to practice. This calls for a different and non-committal approach to innovation, which will make successfully proven PHC solutions the national standard more quickly. An approach in which healthcare providers, healthcare insurers, professional associations, patient associations, medical technology and pharmaceutical companies actively collaborate, with an active directing role by the government.
  - By naming PHC as a national priority, a sense of urgency is established. The feeling that the desired change is really important and urgent is necessary to successfully start the change project.
  - Create room for experimenting (see '**Getting PHC started', 4.4., step 8**), because a sense of urgency is not so much created by convincing others with facts and analyses (analyse-think-change) but rather by experiencing the benefits of change (see-feel-change). The guiding principle for change should be: Just do it'. Experiment, learn, and do it better.

Step 2. Gather a leading coalition: public-private partnership

- Make sure there is a strong group driving the change with leadership skills (driving change), credibility (good reputation), management skills (controlling the process), expertise (to be able to bring change to a good end) and power positions (so that progress is not blocked by those who do not belong):
  - Partners are social parties who are prepared to commit to the joint task and make their contribution;
  - Sometimes the commitment of an employee is sufficient, sometimes the board of the organisation has to formally commit. It is important that the commitment is not (or can become) non-binding;
  - The partners who commit themselves must have sufficient competences to realise this task; we need people who have the sense, knowledge, energy and network to work together on this task and the ability to deal with their mutual differences. But we also need the patience and discipline to take small steps and learn from the results;
  - Any civil society party may join or leave, subject to the commitment made or to be made.

Step 3. Appoint a director: government will direct this cooperation to make it productive

- The government is 'directing without power' in the joint task of accelerating the transition to PHC through the rapid and broad application of PHC in daily practice under socially acceptable conditions:

  - The director is responsible for (a) his/her own actions, (b) the productivity and task orientation of the partnership, (c) the development of healthy relationships between the partners, (d) signalling and putting the right issues on the agenda, (e) the effects of internal and external communication, (f) coordinating the decision-making process in the partnership;
  - The basic principle of directing is that you look for the minimum balance of effort and the smooth running of the cooperation, and that you do not step into the gaps created by partners not taking their responsibility;
  - Direction goes beyond the group of representatives. It also concerns the organisation (the system) from which those representatives come;
  - The government should actively steer where it gets stuck, and at the same time facilitate a lot.

Step 4. Appoint a management team: PHC Catalyst Alliance is available

- Direction requires the ability to spar about strategy and interventions. Therefore, by definition, you need a direction team with different qualities:

  - We present the PHC Catalyst Alliance, a top team of experts, professionals and entrepreneurs within and outside the health domain, who want to accelerate the transition to PHC, have developed a vision on this and have already undertaken the necessary activities. By identifying barriers to implementation, combining brainpower to come up with creative solutions, and making proposals and/or getting to work on concrete pilot projects, the PHC Catalyst Alliance is catalysing the acceleration of the transition to PHC.

4.2 Vision, strategy, action plan

Step 5. Develop a shared vision and change strategy, and draw up a plan of action: 'the PHC National Action Plan'.

- Make it clear how the future differs from the past and how that future can be realised:

  - Characteristics of an effective vision: are imaginable (picture of what the future will look like), attractive (appeals to the long-term interests of all stakeholders), feasible (achievable goals), focused (serves to guide decisions), flexible (leaves room for individual initiative and alternative responses in the light of changing circumstances);
  - Make use of existing plans: for example, the plans of VNO-NCW and MKB-NL 'vooruit met de zorg: beter, slimmeer, en menselijker' and 'vitale mensen, slimme zorg' are largely about PHC. Also make use of the parties that have already committed themselves to these plans;

4.3 Support

Step 6. Communicate intended transition to PHC: use frontrunner adaptations in education, good public campaign, use various communication tools and channels

- Make sure that as many others as possible understand and accept the vision and strategy. It is important that all stakeholders support the transition, propagate it themselves, and are willing to commit to it.

  - **Start by creating a narrow but deep support base:** you also have to learn to play chess. Place every action you take in a broader perspective.

    Use frontrunners
    Radical innovations do not occur in a high frequency. In the case of radical innovations, it is better to focus on 'front runners' who will, in turn, take the team with them. In doing so, they will continually take in information from outside the team, translate it to their own situation and take it along with other team members. The learning style here is therefore focused on the acquisition and processing of completely new knowledge and competences. In radical innovation, work descriptions cannot be used because the processes still change a lot. This means that the leaders have to propagate a strong vision, because this is the only thing that gives direction to the activities of employees.

  - **Building a lobby for PHC:** among citizens, patients, healthcare providers, and investors. This requires a good public campaign and adjustments in the curricula of medical-technical training courses:
    - On behalf of the PHC Catalyst, research was done into awareness of PHC and education in the field of PHC. Based on this, a framework for education has been made per stakeholder group (desired level of knowledge) and a gap analysis has been made (sufficient current education).

  - **Elements in effective communication are:** simplicity, use of metaphors and examples, power of repetition, leading coalition as an example, use of different communication tools and channels, and really engage with people.

4.4 Implementation

Step 7. Enable others to act: remove structural barriers & provide necessary competences and resources

- Remove as many obstacles as possible so that those who want to realise the vision can do so. Provide empowerment by:
  - **Remove structural barriers:** To create an environment in which PHC can thrive, there is an urgent need for systemic measures to remove as many barriers as possible. Use existing solutions as much as possible, for example:

Existing solutions

Dates:

- Ensure that data collected is interoperable and standardised **(EPD)**
- Create opportunities to share data anonymously in the context of public interest **(data donor as an adaptation to the donor law, MedMij, My Data Our Health)**
- Learning from data without touching them or federated learning **(PHT)**
- Create opportunities for data mining **(dynamic consent)**
- Cooperate on the data and compete on the analysis **(HSD2 by analogy with PSD2)**

Registration, reimbursement, inclusion in guidelines:

- Create space for alternatives to build evidence **(n-of-1 trials, Quantified Self)**
- Early access and outcome-based payment schemes **(rolling reviews, conditional admission, Drug Access Protocol)**
- **Multi-stakeholder representation** in guideline committees

- **Ensure needed competences**[xxiii]**:** the successful integration of PHC in the workplace requires highly engaged and trained staff. New knowledge[5] and skills will be required as well as improved digital literacy. Education and training of current and future care workers is therefore the key to success for change.
- **Provide the necessary resources:** it is important that there is sufficient space - in terms of time, money and manpower - for enterprising parties (companies, care institutions) to test innovations in practice, as well as funding for the necessary infrastructure.

The cost goes before the price

To make PHC the norm and apply it on a large scale, investments are needed. But the investor (financially or in data) is not the party who immediately experiences the benefits of PHC ('what is in it for me'). This negative business case calls for other financing models. By investing in the transition to PHC, savings can be made on the healthcare budget and economic growth of the LS&H sector can be stimulated.

- **Reward for innovation:** a good introduction model is needed, where the investor also gets the benefits.
- **Scale-up funding:** resources need to be made available for innovation implementation research. (Government) funding is primarily aimed at innovation as such, but the success of an innovation is primarily determined by social innovation (implementation, embedding and integration in daily practice) and there is little or no funding available for this.
- **Leading by example:** The Netherlands is an attractive location to develop, test and introduce innovations. If we act quickly and are successful, the Netherlands can take a leading role in the field of PHC and create new export opportunities. To achieve this, it is important that we create a PHC home market with stimulating legislation and financing: 'Leading by example'.

[5] Genomics, AI, digital medicine

- **Ensure that information systems are in order:** for example, build a knowledge system to share new knowledge quickly (democratisation of knowledge);
- **Tackle people who undermine change**

Step 8. Generate short-term success: sprint with flagship projects

- Generate short-term successes by carefully choosing your flagship projects. Successes that are visibly related to the change process should be celebrated. The successes show that the vision is working. Celebrating successes rewards those who actively participate in change and provides a counterweight to cynics and obstructionists. Successes develop momentum to continue along the chosen path. Despite the fact that not everything goes right the first time.
  - **Think big, start small, learn fast:** only with a common vision and with small experiments can you navigate through complex issues, always taking into account new external developments;
  - **Focus on the 'low-hanging fruit':** focus on implementing, embedding and integrating existing PHC solutions. Because if we already fail to integrate existing PHC solutions into daily practice, what about the tsunami of PHC solutions still to come?

Getting PHC started

P4-MSJ[iv] method designed by PHC Catalyst Alliance ism Mobiquity and Gupta Strategists
Complex issues are characterised by the absence of a direct cause and effect relationship. This makes it impossible to find unambiguous solutions. The fact that everyone looks at the issue differently and values it differently contributes to this. Only with a common vision and with small experiments can you navigate through such complex issues, always taking into account new developments from outside.

With the P4-MSJ method (**P4**-medcine[xxiv], **M**ulti-**S**takeholder **J**ourney) we make tangible how we can accelerate the transition to PHC for a particular disease. We look at the possibilities from the various perspectives: patient, healthcare provider and healthcare insurer. Their interests may differ. The key question is: 'How to maximize the common good? And how to resolve individual, conflicting interests? The P4-MSJ is specially designed to align the collective and individual interests as well as possible.

The P4-MSJ is implemented in cooperation with Mobiquity and Gupta Strategists. Each co-creation project involves a core team of content experts, patients and Alliance members[6]. In 5 steps, we investigate the MSJ for a specific disorder:

1 **MSJ outline:** each step of the care process is recorded with the core team;
2 **Identifying core frictions:** in the care process, frictions arise in some places. These frictions are similar for all stakeholders in some places, but very different in others. The core team jointly decides which frictions have the highest priority (core frictions);
3 **Analysing trends and PHC applications:** the most important trends and existing PHC applications within the disease area are identified and analysed;

[6] The core team is composed very carefully and consists of people who have the knowledge and energy to work on the subject together and the ability to deal with their differences. But they also have the patience and discipline to take small steps and learn from the results.

4 **Identifying possible solutions:** based on key frictions and trends, possible solutions are[7] formulated to improve the care process. Subsequently, these solutions are measured against P4 - the four dimensions of PHC: Prevention, Prediction, Personalisation, and Participation[8] - to see what the contribution of PHC can be to the solution. The core team then jointly decides which solutions have the highest priority;
5 **Choosing acceleration projects:** through brainstorming sessions, project ideas are generated for the prioritised solution directions. Subsequently, these project ideas are scored on hard knock-out criteria, being: concrete, PHC scope, feasible, scalable, and cashable[9]. The remaining project ideas are pitched to the core team, who choose the acceleration projects. To be able to carry out these projects, external funding needs to be attracted.

So far we have applied the P4-MSJ method twice, namely in rheumatoid arthritis (RA) and in depression. These indications represent the 'followers' resp. 'laggards' category within PHC (see PHC Catalyst report 'n=1, a new paradigm'). We also hope to start a P4-MSJ for breast cancer later this year, representing the 'lead' category in PHC.

For RA, we identified a longlist of 13 frictions resulting in 4 core frictions, from which 7 solution directions were formulated resulting in 5 prioritised solution directions, which then led to 9 project ideas of which 2 were selected to start the acceleration towards PHC: 'precision prediction with patient data' and 'personalised treatment path with smart control'. The outcomes of these acceleration projects are likely to be applicable to other indications as well, as the core constraints play a role within multiple indications.

The above makes clear why innovation implementation is so difficult: 'it is hard work'. Every implementation is tailor-made and requires the stakeholders to work together intensively and to be able to resolve individual, conflicting interests in order to maximise the common good. It also requires the necessary financial resources, which are not easily available: in the Netherlands, there is too little focus on innovation implementation and, consequently, too little funding for implementation research.

For more information, watch the P4-MSJ video and presentations on our website: https://www.phc-catalyst.nl/

[7] Examples of possible solutions: quick access to the right counter (early recognition and referral), illness diary (logbook with self-collected data), deep patient profiling (rich data set based on multi-omics), precision advice (clinical decision tool for determining treatment), signposting (personalised information), customised care contact (care where and when needed), in the cockpit (dashboard for insight into data).
[8] Prevention (in which stages can we intervene prematurely), Prediction (how can we better predict individual treatment response), Personalised (to what extent is it possible to tailor treatment), Participation (how can we better involve the patient)
[9] Feasibility (economic, technical, legal, feasible) and impact (value patient, value healthcare provider, value healthcare insurer).

4.5 Persistence and consolidation

Step 9: Keep up the pace: increase pressure, increase pace, and expand acceleration projects

- Increase the pressure and pace after the first successes. Expand the number of change projects with people who now also subscribe to the mission.

Step 10. Create a new culture: choose development goals, make it fun, and arrange support

- Changes in norms and values come last, not first. Only when they have proven to be better than the old norms and values do they penetrate the culture. This requires a lot of talking to people. Show that successes come from change. Tell how the old culture came into being and why it was successful for a long time but is now no longer adequate. Finally, ensure that the old norms and values are removed from existing processes such as recruitment and selection, remuneration policy, etc.
  - PHC requires a completely different view of diseases, in which we no longer look at the greatest common denominator ('the average'), but instead become curious about the individual differences ('the variation'). In order to realise lasting improvements, it is not enough for people to think differently, they must also act differently, and this often proves difficult. Behavioural research shows that even the development of very simple, self-chosen new habits - such as eating fruit at lunch or doing a few physical exercises before breakfast - takes more than two months on average. More difficult behaviours take even longer.

Why change is difficult and what works[xxv]

Behaviour is the weak link in change:

- **A first important obstacle:** in our brain, two types of processes work against each other. On the one hand, we make conscious plans. On the other hand, our brain is primarily designed for the fully automatic repetition of behaviour that "works" and requires little effort: habitual behaviour. Psychologists say: our brain strives for "cognitive ease": it aims to achieve enough with little effort;
- **A second important barrier is the strong tendency we have to avoid pain, discomfort and loss.** In many cases, this hinders our motivation to learn, to experiment and to make many other forms of change. "Making mistakes is allowed", for example, sounds nice at a management conference. But deep inside our brains there is an ancient, fearful voice warning us: "Making mistakes is just wrong. Don't!"
- **The third important barrier to behavioural change is the physical and social environment in which we move.** A few examples: if people around us nod politely, we talk longer; if we are offered a larger meal or a larger plate, we eat more. Few people realise how much influence their immediate surroundings have. And in an environment that remains unchanged, they still try to achieve new behaviour.

What does work is:

- **Choose your goal:** choose development goals and not performance goals. For all forms of change and renewal, it is essential to realise that it is all about learning: planning, trying, making mistakes, learning a lot, adjusting, and then hopefully scoring; to experience mistakes along the way as learning instead of failure, as a step forward instead of a step back. Therefore, when it comes to change, development goals are more effective than performance goals: not "By the end of this year, I want PHC to be part of daily practice", but rather "In the next six months, I will try at least three ways to accelerate the implementation of PHC in daily practice";
- **Translate it into behaviour:** choose behaviour that you like to bring you closer to your goal. When we see someone achieve an important goal, we often think "what perseverance". The real reason people persevere with certain behaviour is that they simply enjoy the activity. Choose the behaviour that you enjoy the most and it will take the least effort to persevere;
- **Choose your support:** see what you can change in your immediate environment that will make the desired behaviour easier.

5. Recommendations for government and policy

5.1 Recommendations for government

What role can the government play in promoting the implementation of PHC in practice?
The government is crucial in the transition to PHC, because the government enjoys the confidence of all parties (democratically elected?) and the government has the most important tools in its hands (legislation, public campaigns, financial incentives) to actually manage change. The government has an important role as system director, in establishing links between initiatives, in creating the right conditions, in removing institutional obstacles and in providing the necessary resources and competencies. Below, we describe what we specifically ask and expect from the government based on the above-mentioned steps:

- Step 1: **Declare PHC a national priority** to create the necessary sense of urgency;
- Step 2: **Gather a leading coalition** and work together with these social partners on the healthy future.
- Step 3: **Direct** this cooperation to make it productive.
- Step 4: **Appoint a management team** to spar over change strategy and plan of approach.
- Step 5. **Develop your own vision of the transition to PHC** to guide the shared vision/change strategy/'the PHC National Action Plan', and to change with it.

Change of era, the Netherlands tilts[xxvi]
"Social systems are becoming increasingly bogged down. More and more citizens are taking matters into their own hands and forming a movement that will change society. Old pillars are crumbling. The Netherlands is changing from a vertically ordered and centrally controlled top-down society to a society of horizontal relations, where innovations and development take place from the bottom up".
"From past transitions, we know that 20% of the population is needed to bring about a definitive and irreversible change in the system. Tilting players are often atypical people, difficult cross-thinkers, fresh lookers, front runners without whom you cannot transform. Transitions almost always start from the bottom up in society, because vertically oriented politics finds it difficult to really change itself and leaves it at that. In that sense, politics is part of the problem, not the solution".
"It is a misunderstanding to think that politics and government are engaged in fundamental reforms of the labour market, the housing market, education or the energy sector. The agreements that are being made in this framework are mainly adjustments to existing systems, with the same players in the same relationships, but no radical system innovations, no transformative reforms."
"Society is not the sum of initiatives from below. The government must develop a vision of the new economy and the new social and political order and give direction to it and change with it. However, the government cannot organise the transitions, but it can slow them down or speed them up. Acceleration can be achieved by creating conditions, removing institutional obstacles and establishing connections between the many innovative sustainable initiatives from the bottom up. Top sector policy as we know it today does not fit in with this; it is old wine in new bottles. The new economy cuts across all those sectors".

- Step 6. **Launch public campaign** to increase support for PHC.
- Step 7. **Develop PHC policy and ensure coordination of policy** between the various ministries (research (VWS and OC&W), education (OC&W), admission (VWS and EZK), innovation (EZK). **Adapt or clarify laws and regulations** where necessary. **Remove institutional obstacles. Make connections between initiatives** within and outside the Netherlands, because many of the challenges we face are not unique to the Netherlands. **Provide the necessary resources** for the change process, for investments (ICT, data, infrastructure, implementation research, compensation schemes for stakeholders who see their business shrink, etc.) perhaps by setting up an investment fund. **Make adjustments to curricula of medical-technical education** to ensure the necessary competences.
- Step 8. **Choose flagship projects** to generate short-term successes.
- Step 9: **Step up the pressure, step up the pace, and expand acceleration projects** with people who now also subscribe to the mission. Make it fun. Arrange support.
- Step 10. **Share successes** by talking to people and indicating that successes come from change. **Ensure that old norms and values are removed** from processes.

5.2 Policy recommendations

- Develop PHC policies: in line with the directions and recommendations described in the **management summary** and **Appendix 6**.

Personalised healthcare is a paradigm shift in the way we approach healthcare. Putting robust health policies in place can help provide confidence and enable change.

- Policy coherence: the stimulation of knowledge development and the use of PHC in practice is an issue that affects several ministries, and more coherence in the policies of these ministries would be desirable:
  - Stimulating scientific research through ZonMw and NWO (VWS and OC&W);
  - The embedding of new insights in medical education and education for paramedical professions (OC&W);
  - The authorisation and reimbursement of, and trade in, new medicines and medical devices (VWS and EZ);
  - stimulating and regulating an innovative industry (EZ);

5.3 Finally

The guiding principle for change must be: '**Just do it**'. Experiment, learn, and do it better.

Implementation barriers for PHC in the Netherlands

Appendices

Appendix 1: Another view on health needed

1 The Variation Central: Health as a Network Effect[xxvii,xxviii]

PHC calls for a completely different view of diseases, patients and data: it starts with the fact that we no longer look at 'the average', but are curious about the differences between patients: 'the variation is the key'.

Every person is biologically unique
The American researcher Eric Topol writes the following: "That each of us is truly biologically unique, extending from even monozygotic 'identical' twins, is not fully appreciated. Now that it is possible to perform comprehensive -omic assessment of an individual, including one's DNA and RNA sequence and at least some characterization of one's proteome, metabolome, microbiome, autoantibodies, and epigenome, it has become abundantly clear that each of us has truly a one-of-a-kind biological content. Well beyond the allure of the matchless fingerprint or snowflake concept, these singular, individual data and information set up a remarkable and unprecedented opportunity to improve medical treatment and develop preventive strategies to preserve health."

2 Medicine stagnates

There are some obvious problems in treating diseases on the basis of 'the average':

- For example, in **only 30% of cases does** an individual patient **benefit from the medicine he was first given**. The other 70% go home with a drug that does not work for them, and after some time they probably go back to the doctor for another 30%. This trial-and-error approach delays therapy, increases the burden of disease and costs more than three times as much as if a drug had worked immediately.

Take, for example, drug dosage
Historically, people were forced to look at 'the average patient' because there was no way to determine the differences between individuals (at the molecular level). Thus, the dose of a drug is determined by extensive, long-term randomized clinical trials (RCTs). This involves a dose that is safe and effective for 'the average patient'. And that average dose (in fact, often a more than tenfold lower dose so as not to put any individual at risk) is then prescribed to anyone. There is nothing personal about this; it may well be that someone needs or tolerates a much higher dose, while for another even the lower limit is too much. In short, the current recommendations are based on averages based on the response of large groups of people[10] and, while they provide a good, reasonably safe basis, they say nothing about individual needs[11]. People may need more or less, because there is no such thing as 'the average patient'.

- The differences between individual patients also mean that **many potentially useful drugs are not registered** because their effectiveness for the entire population is not high enough, or because their toxicity is too high for a small, unidentifiable group.

[10] The strictly selected patients in RCTs: meet all the inclusion and exclusion criteria of the studies.
[11] Patients in daily practice: often do not meet the strict inclusion and exclusion criteria in studies.

This also means that the costs of developing medicines for the pharmaceutical industry, and therefore for society, are unnecessarily high. And this while the effectiveness and safety for a selected group could well be good.

The reason that good drugs do not necessarily work for everyone is that most diseases are multifactorial, in other words they are network diseases. These networks differ from one individual to another:

- An old paradigm in **pathology** states that a disease is caused by one diseased substance or factor, which then causes a disturbed function somewhere in the body **(reducing complexity to simplicity)**.

- The more modern **(molecular) network approach assumes** that factors can malfunction at different places in a network, ultimately leading to the disruption of one and the same function. This one disturbed function can therefore have completely different causes in different patients. In theory, each patient needs his own (combination of) medicines. In order to make therapy better and more targeted, you will have to understand these complicated molecular networks **(finding simplicity in complexity)**.

The individual differences between people in terms of health, illness and healing thus stem from the differences in the network **(each his own)**:

- Differences in the DNA (due to mutations or a different hereditary background) determine the quality and quantity of the interactions between the different enzymes. If enzymes are blocked or stimulated at crucial places in the network, this can mean that drug A does not work for one person but works for another.

The complexity of human biology is enormous, most diseases are multifactorial, and 'each individual has his own network'. Every patient therefore needs, in theory, his own (combination of) medicines.

3 Systemic medicine is the way to make healthcare sustainable

All steps from molecule, through organ and the complete human being, to a whole population are necessary for a good understanding of medicine. In itself, all these different steps are taken in research, but the **integration of knowledge (the whole is more than the sum of the parts)** is often lacking. This is a must for understanding the complexity of biological systems:

- Classical biology has given us very detailed knowledge, systems biology brings it back together and shows the interaction between all parts. Systems medicine is its application in medicine. It is a method of conducting research, combining all available data. Models are used. The goal is to understand the entire biological system in both disease and health. Systems medicine is a new approach to the personalisation of care.

- In order to provide the individual patient with a treatment that is more effective and has fewer side effects, an integrated approach is needed in clinical research and daily practice. This requires cooperation that transcends areas: clinicians, biologists, modellers, bioinformatics, geneticists and pharmacologists. Cooperation between these highly specialised areas provides insight into interrelationships in the treatment of complex diseases and comorbidity.

- Thinking in integrated networks also requires the researchers involved to network more. This is still somewhat at odds with the prevailing idea that researchers should compete in terms of publications. Moreover, networking also requires cooperation between different worlds: that of the medical profession, biologists, mathematicians and also ICT.

Intensive cooperation between different worlds (integration of knowledge) is needed to understand the entire biological system and to make treatment better and more targeted. This means that 'everyone needs to network more'.

The table below summarises the differences between the current and the evolving medical model.

Table 6.

CURRENT MEDICAL MODEL = 'TRIAL-AND-ERROR' Reducing complexity to simplicity	NEW MEDICAL MODEL = 'PRECISION' (PHC) Finding simplicity in complexity
Parts list	System
Organs (lineair thinking)	Molecular network (network thinking)
Average is leading	Individual differences are leading
One-size-fits-all (trial-and-error)	Tailor-made (precision)
Solidarity: everybody the same treatment	Solidarity: everybody a relevant, appropriate treatment
Treating symptoms	Treating the underlying cause, prevention
Unsustainable sickcare	**Sustainable healthcare**

Watch tip: *do your protein networks have their own social network?*
https://www.youtube.com/watch?v=10oQMHadGos
Network expert and author Albert-László Barabási explains in this TED talk in a simple and visual way that diseases are the result of *systemic malfunctions* in the body, and that mapping intracellular protein networks will help us discover cures.
A picture is worth a thousand words

Appendix 2: Another view on health care needed

1 Current healthcare system is not sustainable

In the Netherlands, we spend over 87 billion euro annually on collectively insured care. Together with social security, healthcare is the largest cost item of the Dutch government. Not only are healthcare costs high, but they are also constantly rising. The cost of healthcare is rising faster than the national income. This increase is caused by a double aging population, an increase in chronic diseases, and new medical technology. In addition, there is a growing shortage of personnel. These factors are putting pressure on the healthcare system.
According to the RIVM, in the not-too-distant future there will be seven million people in the Netherlands with chronic diseases. These include physical conditions such as type 2 diabetes, cancer, cardiovascular diseases and psychological conditions such as dementia, depression and anxiety disorders. And then there are the large numbers of people who are treated with medication for risk factors for diseases such as high blood pressure and high cholesterol.
These huge numbers of sick people will cause healthcare costs to rise from 87 billion to 174 billion in 2040. This means that a family will spend half of its income on healthcare. This is not sustainable. In addition, rising collective healthcare costs are crowding out other government expenditure. Less investment means less economic progress and therefore less prosperity.

2 Different view on healthcare needed

As the population ages, the number of chronically ill people increases and the number of advanced treatment methods expands rapidly, a different view of care becomes necessary if we are to keep the exploding costs of care under control.
We need to control healthcare costs and at the same time improve care, because better care increases the quality of life, our well-being, as well as labour participation and productivity. Obvious economic benefits.

3 Government and social partners work together for a healthy future

To achieve this, the government and social partners must join forces. A collective investment is needed: not only financially, but also behaviourally and organisationally. Working together for a healthy future: 'Growing old healthily'. Care back to the core:

- Only necessary and appropriate care will be charged to the collective. Extra care must be purchased personally. People can save up for this, take out extra insurance, etc;
- Citizens can also invest in themselves by adopting a healthy lifestyle: no tobacco, no drugs, metered alcohol intake, more exercise and healthier eating;
- Productivity and efficiency in healthcare must also be optimised.

What are the concrete steps to be taken in line with this different view of healthcare?

Prevention is better than cure

- Many of today's health problems are diseases of affluence, which can best be combated by eliminating smoking, excessive alcohol and drug use, physical inactivity and excessive consumption of unhealthy food ('an apple a day keeps the doctor away'), and only to a limited extent by more curative and long-term care. A better public health therefore starts with *a better living environment*, which enables us to prevent or postpone diseases and which makes it possible for people with illnesses to live healthier lives with fewer complications.

Hit hard, hit early

- The consequences of incipient diseases can be relatively easily prevented or postponed *at an early stage*. Waiting until a disease becomes so serious that intervention with heavier artillery is necessary is unwise from a medical-ethical and financial point of view. Yet that is what regularly happens.

Personalise where it (already) can":

- The future of healthcare will increasingly depend on identifying and correctly interpreting the earliest signs of disease susceptibility, and thus preventing, diagnosing and treating disease *on an individual basis*. This will enable people to live healthier and older.

Radically cut out nonsensical care' & 'Promote healthy behaviour'

Financial scope must be created for prevention, early treatment and personalised treatment. This can be done by *radically scrapping nonsensical care and by promoting healthy behaviour:*

- Medical treatments that make no sense are a silent killer. Because pointless treatments cost money and time, leaving less room for treatments that do make sense. Changing senseless care is more than changing medical practices; you have to change the whole environment, and that takes time[xxix,xxx]. It depends on the will of doctors and practitioners. To force change, the government and insurers have to balance between being compelling and not giving the healthcare sector the idea that a diktat is being imposed on them. If you force something nationwide, you run the risk that doctors and hospitals no longer feel responsible. It is much better to help the frontrunners, the hospitals that have already implemented sensible care. Front runners set the tone.
- Unhealthy behaviour leads to poorer health and this deterioration results in higher healthcare costs. Less non-committal measures are needed to make healthy living more attractive and easier for people. This requires targeted cooperation between the various ministries and that health insurers and municipalities not only fulfil a duty of care, but also a duty of health.

Appendix 3: Innovation paradox & the last mile

There are numerous definitions of innovation. In this report, we use the following practical description:

Innovation is a process of creating value by using knowledge and other resources in a way that has not been done before.

A number of words in this definition play an important role:

1 **Process:** innovation is a process in the sense that it involves input (ideas, experiences, resources), activities (R&D, (technical) realisation, market introduction, etc.) and output (product, service, new business model, etc.). Generally, recognisable steps can be identified.

2 **Value creation:** innovation is not just about something new, but about a development that has an experienced value for those involved. This value does not have to be (exclusively) financial, but can also relate to health, happiness, convenience, a better society, a cleaner environment, an increase in knowledge, new relationships, and so on.

3 **Use of knowledge and other resources:** In point 1 we already stated that innovation is a process in which input is converted into output. The input often largely takes the form of ideas, information and insights; these are the constituent parts of knowledge. This knowledge can be found within the organisation, but it can also be (partly) acquired from outside. The origin of the knowledge may even lie outside your own sector. Whatever organisation you work for, the fact is that there is much more knowledge outside than inside (unless you work for an organisation with approximately 7.4 billion colleagues...).

4 **New ways of using things:** Of course innovation has something to do with 'new'. This is obvious when we look at the meaning of the Latin word innovare, which means 'to renew' or 'to change'. But not everything that is new can be qualified as innovation. For that, according to point 2, value creation (financial, social, intellectual capital) is needed. And this value creation is, of course, only realised when the innovative concepts are applied.

How can we ensure that efforts and investments in the area of innovation and entrepreneurship have maximum effect? Answering this question is of great importance. And that is badly needed, because research shows that the 'innovation paradox' is persistent. This means that the gap between the priority given to innovation in the Netherlands and the money invested in it is still large. This has particularly negative consequences for the last phase of the innovation process, the scale-up, commercialisation or implementation. And without that last step, there is no value creation, which leads to growing frustration and makes innovation less and less popular.

In order to support and accelerate the last step in particular, various methods are being developed and applied (so actually also (system) innovations...), whereby parties are sought out and connected in various ways to help promising innovative developments in the 'Last Mile': the step from 'Proof of Concept' to 'Proof of Business', or the scaling-up phase.

In this report we see that in the complex care system with often conflicting interests and mechanisms, various barriers stand in the way of a fast(er) transition to PHC.

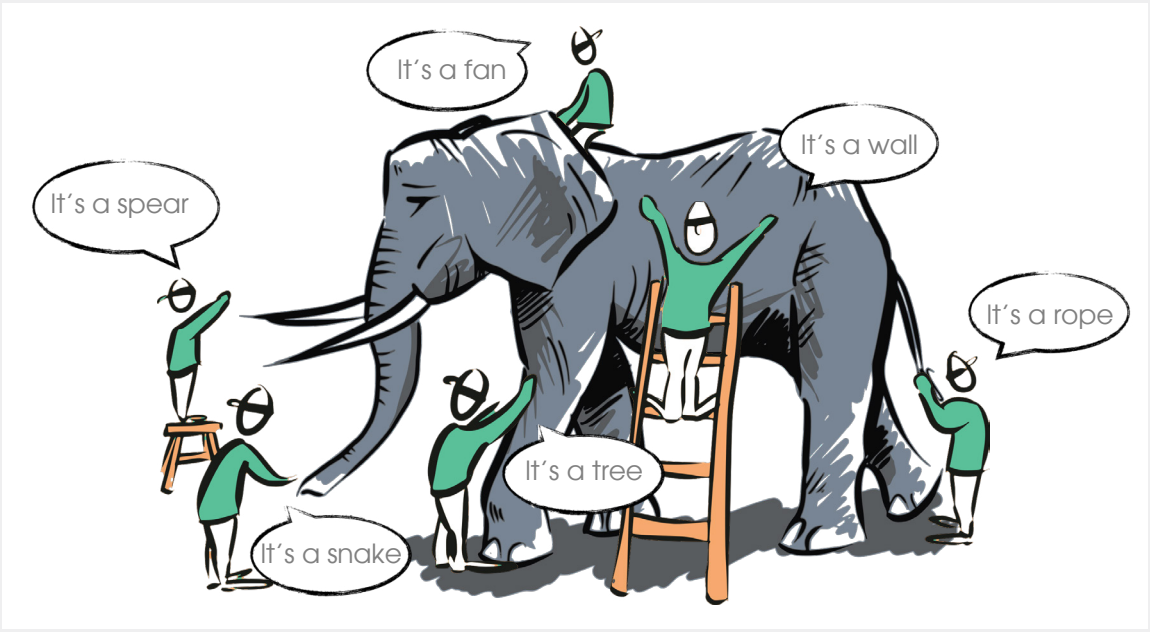
Complexity and paradigm shifts are found primarily, but not exclusively, in transformative innovations. In 'The Innovator's Dilemma', Clayton Christensen gives a good description and many examples of disruptive innovations with major impact on established companies and even entire sectors. As already indicated, it is becoming increasingly important to share and combine knowledge. However, due to the complexity, there is no guarantee for (immediate) success. Side effects, long-term effects and weak signals are ignored or not understood at all. In such a context, serendipity often occurs, which we can best describe as the talent to make valuable discoveries without specifically looking
for them. Various authors, including Prahalad and Krishnan in their book 'The New Age of Innovation', state that in the coming years, more innovation can be expected based on new, collaborative business models, compared to (mono disciplinary) product development. "Open innovation is the use of purposive inflows and outflows of knowledge to accelerate internal innovation and expand the markets for external use of innovation, respectively. This paradigm assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as they look to advance their technology", according to Henry Chesbrough in 'Open Innovation, Researching a New Paradigm'. Thus, Open Innovation focuses on the targeted acquisition of knowledge to solve identified problems. It can thus be described as: "A problem in search of a (compound) answer". What if we turn this around? To this end, we define a Combinatorial Innovation as a new category of activities that lead to innovative value creation:

Combinatorial Innovation is the process of discovering new forms of value creation through the combination and application of hitherto unconnected intellectual capital.

The basic mechanism behind Combinatorial Innovation is the extension of configuration spaces, within which the identification, explication, exploration and understanding of new categories of concepts, problems and solutions can take place. Combinatorial Innovation is the core process of the PHC Catalyst Alliance!

It is important that we address all aspects of the transition to PHC.

Think of the well-known story in which six blindfolded people touch an elephant. When asked what object they think they are dealing with, they give very different answers, depending on the part of the elephant they are touching. However, when they share and combine their observations, the elephant 'appears'. In complexity theory, this phenomenon is called emergence.



And so it is with the solutions that are sought for solving the innovation paradox: they usually 'appear' when the right parties are involved.
Here it is important to distinguish the following different relevant groups:

a) Financiers:
- public financiers: national (EZ, O&W) and European government bodies and science organisations such as NWO and STW.
- private financiers: banks and investment companies, companies and business clusters or umbrella organisations

b) Knowledge institutions; focus: knowledge generation
- Universities including research schools and institutes of excellence
- public and/or private research institutes such as TNO, ECN, CBS

c) Business and government organisations; focus: knowledge application
- companies
- public-private partnerships
- government organisations

d) Governmental organisations; focus: legislation and regulation, stimulation
- European authorities
- Government
- authorities/supervisors

e) (Representative representatives of) Citizens

In many PHC projects, parties must be identified and involved in creating a 'collective business case'. This is not just about financial value creation, but various stakeholders will have different interests and will look at the concept of value differently. At each step in the transition process, the stakeholders will consider their interests: they will create their 'Value Case', in which a combination of three forms of capital will be transformed into a new combination. These forms are: A. Economic Capital (money, property) B. Social Capital (health, safety, nature), C. Intellectual Capital (knowledge, networks, processes).

Figure 6. Different forms of value

From Business case to Value Case

Financial value
Societal value
a. Social capital
b. Natural capital

Intellectual value
a. Knowledge capital
b. Relational capital
c. Structural capital

Nowadays one also speaks of ESG: This abbreviation stands for Environmental, Social & Governance. It means that factors such as energy consumption, climate, availability of raw materials, health, safety and good corporate governance are taken into account in the selection and management of investments in companies.

Where companies have room for improvement in this area, private equity is ideally suited to seizing these opportunities and simultaneously making a positive social contribution, not only to profit but also to people and planet. The entire investment process - from selection to exit - offers opportunities for sustainability.

ESG stands for the search for a balance between financial economic results, transparency, social interests and the environment without losing sight of the balance between them. Contrary to popular belief, this balance leads to better results for both the company and society. There is a broad consensus that ESG objectives ultimately create added value for portfolio companies, both in terms of risk mitigation and value creation. In addition to investors, the government often pays considerable attention to ESG.

Appendix 4: Archetypes of brilliant failure

The Institute for Brilliant Failures has developed a number of Archetypes for Brilliant Failures; patterns or learning moments that transcend a specific experience and can also be applied to many other innovation projects and processes. These Archetypes can be directly linked to the risk of failure of a network. In the interviews, the archetypes were used as a steppingstone to shape the conversations and to ensure that all learning aspects could be addressed.

1. The elephant - the whole is more than the sum of its parts

Make sure there is enough diversity in the network to be able to consider the issues from all angles. Especially in the case of complex issues, the best solution often lies in combining perspectives.

2. The empty space at the table - not all relevant parties are involved

If not all relevant parties participate, the result may not be supported by the field in question and everything may have been for nothing.

3. The wrong wallet - one man's advantage is another man's disadvantage

When funding of network activities puts pressure on other funding, it can create a problem for the commitment of parties affected by it (strategic fit).

4. The winner takes it all - room for only one solution

Find out whether the network has competitors and whether there are alternatives to the solutions offered. There may also be competition within the network. Pay attention to that.

5. The canyon - ingrained patterns

If change is the aim of the network, bear in mind that some parties may have difficulty with that. Especially when evidence-based working is the norm. Also, try to vary the steering or approach of the network if there are signals that it is not going optimally.

6 The right hemisphere - not all decisions are made rationally

A network is formed by people and you cannot always know what is going on in the heads of those people. In collaborations, non-rational positions are sometimes taken or factors unknown to others play a role.

7 The Black Swan - unforeseen developments are part of the game

Keep in mind that external factors beyond your control can affect the success of the network, such as policy changes, new budgets, change of management, etc.

8 The banana peel - an accident is in a small corner

Especially in the operational aspects of network formation, small things can eventually play a big (negative) role. Think, for example, of signals that indicate that there is not enough commitment on the part of one or more parties. Observing and acting on 'weak signals' can prevent bigger problems later on.

9 The bridge of Honduras - problems move on

Everything is in motion. Remain alert to the fact that a problem in network cooperation may seem to have been solved, but may manifest itself in a different way at another time. New reasons may emerge that put pressure on the cooperation or that introduce new problems into the results or solutions achieved.

10. The bear's skin - concluding too quickly that something is a success

In the beginning, everyone is in good spirits and the "low-hanging fruit" is picked. This is no guarantee for continued good functioning. Pilots are often organised in controlled, not necessarily representative environments. Scaling up/implementation is often the challenge. After a while, the commitment can sink in. Take this into account.

11. The Einstein point - dealing with complexity

It is not easy to make a network function really well, but don't make it unnecessarily complicated with all sorts of detailed agreements, contracts, start-up documents, etc. Agree with each other on the essentials and get going. Do evaluate every now and then. Try to subdivide complex subjects into manageable parts as much as possible and, where that is difficult, make the approach as agile as possible.

12. The light bulb - experimenting

In innovation, one is looking for answers to questions and sometimes even the questions themselves. Discuss where this is the case and accept that the results may be disappointing. This is not a failed experiment, but rather a successful one in order to find out more.

13. General without an army - the right idea but not the resources

Make sure you have the resources to actually realise the plans of the network.

14. The junk - the art of stopping

When unexpectedly a network activity, or perhaps the network itself, does not deliver what was hoped for, do not wait too long to intervene.

15. The diver from Acapulco - timing

Make sure that the network does not get off to a fast start and does not come up with plans and activities that the environment or the parties involved are not yet ready for. But also make sure that cooperation does not start too slowly and that activities/results come too late.

16. The farmer's daughter - the art of accidentally discovering something important

Serendipity is an important process in complex environments. Keep looking for unexpected opportunities to add value to the network. Sometimes opportunities arise that you had not originally anticipated. While looking for the proverbial needle in the haystack, you may discover the farmer's attractive daughter.

Appendix 5: *Own* value cases … 'What is in it for me'?

(A) Patient/citizen perspective

The value that this stakeholder is looking for is, of course, the preservation/recovery of health. In addition to money (directly or indirectly through health insurance or community funds), the patient mainly has the sharing of data to offer. This may involve data in certain (medical or non-medical) systems, but also personal data, such as data collected via wearables.

(B) Perspective of the healthcare professional

The primary objective of the healthcare professional is to provide good care. In addition, the professional naturally has a financial interest in the continuity of his activities and his own existence. In working towards this goal, he/she requires information from various sources: from the patient himself, information about the patient (medical dossier), information about treatment methods (medicines, treatments, equipment), about the laws and regulations surrounding the treatments, including financing. The professional also generates information that can and often must be shared, such as the result of the treatment. The sharing of information is often mandatory, for example for financing, quality control or general interest of the knowledge concerned. If an extra effort is required, the motivation will have to come from an intrinsic drive to improve care, a financial incentive to justify any extra effort, or access to information relevant to the professional's practice.

(C) Perspective of the researcher/scientist

The primary process of the scientist is to conduct research. The aim is to generate and validate new insights. Besides the scientific ambitions, the scientist also has a financial interest. The knowledge produced during scientific research acquires value when it can be applied. Therefore, sharing and combining with other knowledge is important. Sharing through publications is often a requirement for the providers of funds and contributes to the position of the scientist. However, the unrestrained sharing of data obtained from research can weaken the position of the scientist: other researchers may use the data to obtain support (grants) for their own research and the person who shared the information may be subject to de facto competition on the basis of his own knowledge/information. This is partly unavoidable in science, where progress depends on building on each other's work. But it may also be better locally not to share all data in order to build up a competitive advantage. In fact, a form of 'prisoners' dilemma'. In order to share the data, the scientist seeks compensation in the form of money, relevant data from others or a strengthening of the scientific position.

(D) Perspective of the management of care/knowledge institutions

The management is responsible for the sustainable functioning of the organisation. This requires people and resources. For a working data infrastructure for PHC, information systems must be redesigned and linked. This involves processes, information models and technical resources. Here, too, the costs may outweigh the benefits and there may even be a threat of a 'wrong wallet', where the financial benefits do not outweigh the investments. Also in the area of change management (staff motivation), changes in business operations can cost time and money. If the position of the organisation's employees is affected (financially or non-financially), this can have consequences for the organisation because people may leave or provide more return for the organisation. On the other hand, producing and sharing information can mean a new revenue model.

(E) Payer's perspective

In principle, the payer of health care will always strive for an optimal ratio between the health gains achieved and the associated costs. However, there are a number of factors that complicate this in a dynamic and complex environment. Long-term and short-term thinking play a role in this. For example, investments must be made in the creation, collection and sharing of data without being sure a priori which information is relevant. However, the costs of data/knowledge management are real and often immediate. In the case of PHC, the acquisition of new insights will partly take place in an exploratory manner ('data mining'), whereby increasing the efficiency of care can only take place by accepting costs that do not directly lead to health gains in the environment or with the patient where the knowledge or information is generated. The decoupling of investment and return is a well-known problem in research and subjects such as prevention. This dilemma can only be solved at the system level. In any case, the payer will only be willing to finance knowledge building and dissemination if he can make a positive business case for it within the horizon of decision-making, or if pressure is exerted and/or support is provided from outside.

(F) Government's perspective

The government is an important financier of (developments in) healthcare. In addition, the government often has the role of system owner (sometimes against its will), which means that the government can exert considerable influence on the incentives and rules of the system. The government could, in particular, have a driving and facilitating role when it comes to long-term value creation, which is inherent in the transition to an entirely new healthcare system, based on (more) PHC. This means that the economic component of the value case may initially be negative, particularly for the government and other parties responsible for the system. Through subsidies and other incentives, the government can (partially) compensate for the negative consequences for parties within the system. On the other hand, over time this will result in a healthier population, in which certain healthcare costs will be lower, among other things due to shifts from 2nd to 1st line and also to 0th line (patients themselves). In addition, a healthier population is also more productive.

The government is therefore also an important party in establishing and enforcing the rules, which can be both 'protective' and 'enabling'. A good example of 'enabling' is the European legislation on privacy, the GDPR (General Data Protection Regulation), elaborated in the Netherlands in the AVG (General Data Protection Regulation). At first glance, this seems to be a set of restrictive rules, mainly associated with violations and associated fines. But actually, the rules indicate when something is allowed. It is rather in the interpretation and the way in which the rules are dealt with that the limitation lies. A good example is the directive PSD2 (Payment Service Directive 2) that has been active in the financial sector for a few years now. This regulation, which is intended to accelerate innovation, stipulates that the customer has control over his or her data and that, at the initiative of that customer, the service provider (usually a bank) must share that data with other service providers according to the FAIR principle (Findable, Accessible, Interoperable, Reusable). This puts the customer in control and allows innovations to take place on the basis of shared data. In fact, in healthcare we need a similar regulation and corresponding infrastructure, so let's strive for an HSD2: Health Service Directive 2.

More efficient use of data will also save a lot, both in the development and maintenance of infrastructure and in reducing waste in the creation of knowledge (R&D) and the faster application of the developed knowledge. Through new forms of investment and risk sharing, such as Health Impact Bonds, the government can create more impact with fewer resources.

The role of government as (co-)financier of innovations is also important. Healthcare is a very important sector economically. In 2019, the Netherlands spent EUR 80.9 billion on healthcare, which is approximately 10 percent of the gross domestic product. This is comparable to the percentage of healthcare spending in Norway, Denmark and the United Kingdom. Switzerland, Germany and France spent the most on healthcare as a proportion of GDP. This percentage puts the Netherlands in 10th place in a list of 31 European countries. But in addition to the costs, there are also benefits. By investing in companies, participating in them and allowing the revenues (financial, employment) to benefit the Netherlands, healthcare can also make a direct positive contribution, in addition of course to the positive economic value of a healthy (working) population.

(G) Business perspective

The business world is difficult to pin down. We are dealing with companies that are active in the primary processes, such as pharmaceutical companies, suppliers of medical technology, service providers. In addition, there are also companies that play a role in the knowledge and information infrastructure. And here we distinguish both the parties with the content (databases) and the ICT companies that develop and maintain the technical infrastructure. Identifying and exploiting opportunities is in the DNA of an entrepreneur. For most companies, a new development also means new opportunities. New product-market combinations may emerge, which can provide new business models or help scale up existing earning models. For some branches of business, however, developments mean the end of existing business models and those activities will have to be terminated and/or replaced by new ways of creating value.
The smart use of data also means a reduction in costs, and the better use of (each other's) information provides more opportunities for generating income and other forms of impact.
By analogy with a stock exchange (the first of which was established in the Netherlands, with the aim of democratising ownership of the VOC, and which played an important role in the enormous economic development of the 17th century), a 'data exchange' can play an important role in facilitating the exchange of data. Parties that invest in the collection and maintenance of data can use the exchange to valorise their efforts and thus create new revenue models, while others can use the same data in their own way to achieve upscaling and/or innovation.
The Dutch ecosystem must be used to build up a competitive advantage over other areas, just as in horticulture. This is in line with the philosophy as expressed in the Top Sectors policy. But it is primarily up to the companies themselves to find out where the opportunities lie.

Appendix 6: Challenges for precision medicine

Data	
Barriers	• **Collection of good quality data needed** High degree of data fragmentation; practical barriers in the workflow; ICT barriers; unclear what data needs to be collected; data quality (FAIR, FACT); • **Data sharing mostly limited** Access to different data sources needed to upgrade PHC (data mining); currently 'silos of scattered stand-alone databases'; • **No national data infrastructure** Very many separate data initiatives, but no specific initiatives to promote implementation of PM in daily practice; in time, Health-RI could be suitable, but the focus of Health-RI is on research and not explicitly on implementation in care and/or support and substantiation of funding; the challenges for Health-RI lie in obtaining broad support, in the great variety of types of data, and in direction and governance (more than 60 organisations connected); • **No EHR**[12] In the future, by linking to 'personal health records', information about health effects could be generated that would be of interest for research, implementation in care and package measures and reimbursement. In the Netherlands, MedMij is interesting in this respect: this initiative aims to create an online personal health environment, in which every citizen can retrieve their own data from various sources, manage it and release it for research purposes.
Conclusions	• Setting up large-scale data infrastructures for PM is complex and requires the involvement of many parties and disciplines.
Recommendations for government policy	• **Encourage improved data collection and application for the purpose of applying PM in medical practice** Think of having standards drawn up for the collection of data that may be important to PM: clinical sampling, analytical tests, data analysis, data interpretation, data storage, data exchange, data visualisation for use by practitioners and patients; • **Work towards eliminating and/or preventing the fragmentation of data initiatives, and ensure that control over the realisation of data infrastructures is clearly laid down** Preferably by an independent party with broad support; • **Ensure that data can be made available for future implementation and reimbursement purposes;**

[12] Electronic Medical Record (EMR) is a digital version of the paper charts used previously and is only accessible by a single healthcare provider. Electronic exchange of data with other HCPs is not possible. The Electronic Health Record (EHR) is a more advanced system than EMR. An EHR contains the data of all the HCPs involved in the treatment of a patient and all the involved HCPs have access to this information.

Research & Development	
Barriers	• **Scientific knowledge of PM is limited (in development)** Genotyping is not the only factor involved, there are often many factors that influence the effect of pharmacotherapy on an individual and there is still much unknown about the influence of all these factors and their interaction on the expected therapeutic outcome; • **Targeted scientific research needed** Further refine current knowledge on disease mechanisms, PM diagnosis and PM interventions; develop new methods and techniques for research on small numbers of patients or the individual; • **Little implementation research and insufficient interaction between research and practice** There is a gap between scientific research and application in practice: no translation is made from research to application in practice (because there is a lack of time, money, and knowledge and skills to translate research into practice); linking data from clinical practice with research data can yield new knowledge (this is particularly important for patients with more complex problems), but feedback as to whether genotyping and the associated treatment recommendations have also helped is not a standard part of the routine process of the therapists; • **Increase in width needed** PHC innovations are increasing, but for the time being they are mainly concentrated on oncology;
Conclusions	• Further refine current PM knowledge and close the gap between science and practice.
 Recommendations for government policy	• **Prioritise use of research funds** Identify priority areas (diseases, diagnostic tests, drugs); prioritise based on potential clinical benefit; ensure that reward system researchers focus not only on obtaining publications but also on practice changing. • **Ensure more attention for (and joint financing of) implementation research in the field of PM** both from government researchers and subsidy providers, and from other interested parties, such as health insurers and pharmaceutical companies (for financing implementation research, bring together sources from government, health insurers and pharmaceutical companies). **Start a process to intertwine research and practice more closely** So that data from clinical practice can be more easily used for research and research results can be used more quickly in clinical practice; **Provide knowledge and skills to translate research into practice**

Market authorisation	
Barriers	• **It is difficult to fit PM into a system where EBM and large RCTs are decisive for registration, reimbursement, and professional guidelines** As knowledge increases about the (many) factors that play a role in the effect of drugs on a condition, it will become increasingly difficult to conduct clinical trials with sufficient conclusive power according to current standards (RCTs). After all, large RCTs cannot be conducted with small patient populations. These limited possibilities for RCTs lead to the expectation that much more reliance will have to be placed on data collected in daily medical practice (RWD). This requires requirements for the way in which data is collected and exchanged: it must be clear which data needs to be collected, the independence and quality of the data must be guaranteed, links must be established between (international) data sets; at present, data from patient registries often still varies too much between registries or is collected at too high a level of aggregation to serve as evidence; • **Early admission and speed of admission leave much to be desired** In addition, there is increasing social pressure for early and rapid access to innovative medicines.
Conclusions	• The sustainability of the market authorisation system is under discussion.
Recommen-dations for government policy	• **Other type of evidence needed for the individual = 'n-of-1' clinical trial** Investigate how changes in the quantity and nature of clinical data affect market authorisation systems, Reimbursement and financing of care. Check whether there are any obstacles that could ultimately prevent or delay the application of PHC; • Invest in the **expansion of SmPCs (via EMA or Heads of Medicines Agencies)** of existing medicines with trade perspectives in case of genetic variations, if these are known and supported by scientific evidence. Also consider how SmPCs can remain up-to-date, as knowledge in this area is rapidly increasing and changing.

Implementation in clinical practice	
Barriers	• **Insufficient evidence of clinical benefit** Clinical benefit (degree of improvement in clinical outcomes) depends on, among other things, the severity of the disorder, the availability of alternatives, and cost-effectiveness. There is currently no (international) consensus as to what level of evidence is necessary to make the clinical benefit plausible; no direct relationship between genotyping and treatment outcomes; clinical outcomes may be ambivalent; • **Lack of clarity regarding the context of application** Test properties; target group; caregiver responsibilities;
Conclusions	• Consensus needed on what type of data is needed to demonstrate clinical benefit and cost-effectiveness of PM
 Recommendations for government policy	• **What type of data is needed to demonstrate clinical benefit?** Direct ZiN, in consultation with CBG, other stakeholders and experts, to produce recommendations on the type of data needed to estimate the clinical benefit and cost-effectiveness of the application of pharmacogenetics. In doing so, include European and international developments in the recommendations; • **Which clinical outcome measures are considered relevant for registration and reimbursement?** This possibility already exists: both pharmaceutical companies and research institutions involved in translational drug research can request scientific advice from the MEB. This can be a combined request for advice with ZiN. • **What are the requirements for data collection in practice as an alternative to RCTs?** The relevance and reliability of the data must be unquestionable, and the fragmentation of data also deserves attention (see the recommendations under data infrastructure)

Adoption in clinical practice	
Barriers	• **Knowledge plays an important role in whether or not it is used in clinical practice, both for diagnosis and treatment.** A distinction is made between the collection of scientific knowledge about PM, the processing of this knowledge in, for example, guidelines, and the knowledge that care providers and the public themselves have about the possibilities of PM in diagnostics and treatment: **(a) Available scientific knowledge and translation into practice** The expectations of PM are high, but are tempered by the available scientific knowledge. And if the scientific knowledge is available, it often turns out that it has not been translated into medical practice, for example because of the lack of data to support its clinical usefulness. **(b) Not included in treatment guidelines** Much PM research is not 'practice changing'; translation of research to application in practice is often lacking; insufficient evidence for inclusion in guidelines, which are based on 'state of the art science and practice'; **(c) Limited knowledge of practitioners about possibilities and applications** Lack of knowledge about genetics hinders the acceptance of pharmacogenetic tests: difficulty in knowing when to request a test and for which patient, and difficulty in interpreting the results of a test; • **Limited experience of practitioners** Whether or not PM is used in diagnostics or treatment also depends on the extent to which practitioners are familiar with PM applications. Within a hospital there is often a small group of doctors who work with PM applications, such as genotyping. This group knows very well what they can do with the tests. Doctors who do not know, do not request tests; • **Restrictive beliefs of practitioners** Even though clinical benefit has been demonstrated, healthcare providers have yet to be convinced; • **Other obstacles around application** Obstacles to funding and reimbursement of PM diagnostics and PM treatments; no clinical decision-making support using clinical decision support tools; turnaround time of pharmacogenetics test too long or interferes too much with the routine process; patients in clinical practice are often more complex than assumed in studies, e.g. patients with multimorbidity, polypharmacy, and/or renal and liver function disorders; lack of necessary multi-disciplinary cooperation (e.g. medical specialist, geneticist, bioinformatician, pathologist, radiologist, pharmacist). Lack of necessary multi-disciplinary cooperation (e.g. medical specialist, geneticist, statistician, bioinformatician, pathologist, radiologist, pharmacist) • **Unfamiliarity with PM among patients and the general public** Limited patient/public pull

Conclusions	• Little is said about PM in treatment guidelines.
 Recommendations for government policy	• **Encourage inclusion of practitioners in professional guidelines** so that application in practice is promoted. The clinical benefit should be considered; guideline developers should pay more attention to the available knowledge on PM; optimise the input of experts in the working group that draws up guidelines; • **Treaters, pharmacists and nurses should be trained (more extensively)** to generate pharmacogenetic data (and other -omics data), to interpret it, and to translate it into treatment decisions. Training is also desirable to discuss the pros and cons of a genetic test with a patient; prepare for the developments around PHC; ensure that besides pharmacogenetics, systems medicine is given a larger place in medical education; • **Training of data management experts and bioinformaticians** to enable interpretation of large data sets • **Increase public awareness and understanding** Regarding the possibilities and limitations of genetic testing; patients can also be better equipped to make informed decisions about whether or not to have genetic characteristics tested for PM. Erfocentrum has information on pharmacogenetics on their website;
 Other recommendations	• **Importance of peer pressure** If a PM application is adopted by enthusiastic doctors within the profession ("front runners"), other doctors often follow suit; • **Reduce obstacles to the application of PM** Reimburse PM diagnostics and treatment; bring knowledge and trade options together at the time of prescription using clinical decision support tools; strategic approach needed for turn-around time, e.g. test facilities nearby or patients already tested before they see the doctor.

Funding and reimbursement	
Barriers	• **Financial structures in the health care sector still offer little scope for funding and reimbursement of PM diagnostics and treatment** Reimbursement is essential for implementation; PM diagnostics and treatment are seen as more expensive than traditional treatment and testing: in general, costs of new technologies are initially high, but then quickly decrease due to increased volume (wider use) and competition; • **Adequate evidence** **(a) Lack of cost-effectiveness analyses** The high price of PM drugs is often at odds with the low strength of the clinical evidence due to the smaller patient groups; the tension between cost and burden of proof also recurs in PM diagnostics (and prevention of deaths is weighted differently than prevention of side effects); **(b) Field, health insurers, and government are waiting for cost-effectiveness evidence, but this evidence will not come without application** Application and evidence are, as it were, hostage to each other: evidence is hampered by the relatively small patient groups; furthermore, cost-effectiveness is difficult to determine because it is strongly dependent on volume; **(c) Lack of relevant data for cost-effectiveness analysis** Data relevant to cost-effectiveness analyses should be collected in greater detail, such as data on clinical effectiveness, clinical utility and changes in health outcomes; • **Saving care costs** There is debate as to whether the application of PM is (ultimately) really cost-effective in practice; • **Unclear reimbursement rules for PM diagnostics** Sometimes it is covered by hospital costs and sometimes by the patient's health insurance; it can also depend on who has requested the test, and on the health insurance company; • **Unfavourable earnings model for pharmaceutical companies** Drug development for small groups of patients is not financially attractive.
Conclusions	• PM diagnostics and PM treatment are mostly not reimbursed
 Recommendations for government policy	• **Government should provide clarity on criteria for admitting diagnostic pharmacogenetics tests to the health insurance benefit package** ZiN takes this up • **Discuss obstacles to funding and reimbursement of PM diagnostics and treatment** Consult with health insurers, Zorginstituut Nederland, hospitals and primary care about how the obstacles are experienced and how they can be solved.

Ethical, legal, and social implications (ELSI)	
Barriers	• **Lack of laws and regulations and/or lack of clarity about the coherence of laws and regulations that apply specifically to PM** Dutch laws contradict each other; this is because different parts of PM fall under different regulations, creating grey areas; lack of clarity about (upcoming) laws and regulations that affect research into and application of PM, such as laws and regulations on privacy, personal data and control over body material; insufficient harmonisation between the US and Europe; • **Concerns in particular about privacy and confidentiality, informed consent, and control over body tissue** Who has insight into the data? Who owns the data? Who is liable if something happens to the data? Classical model of informed consent is not adequate for PM; further issues include the right to 'not know', the lack of action perspectives, and the blurring of boundaries between basic scientific research, clinical studies, diagnostics and screening.
Conclusions	• Lack of laws and regulations and/or lack of clarity about the relationship between various laws and regulations that apply specifically to PM
 Recommendations for government policy	• **Investigate which laws and regulations apply specifically to PM** Consider whether there are obstacles that could ultimately prevent or delay the application of PM. There is a need for functional, nuanced, agile legal and ethical responses that simultaneously protect individual rights and enable the progress of science and medicine. Harmonisation is needed between the US and Europe (e.g. requirements for clinical studies, inclusion of information on pharmacogenetics in the SmPC). Involve broad circle of stakeholders to prioritise problems and how they can be jointly addressed
 Other recommendations	• **Informed consent model needs to be adapted or replaced by another paradigm**

Appendix 7: Manifesto prepared by PHC Catalyst Alliance

If we can do better, we must do better

Manifesto for personalised healthcare for every person

Dutch healthcare is among the best in the world. We can be proud of that, as a country and as citizens. The fact that this high-quality health care exists is because we have constantly taken new steps into the future.

If you can do better, you must do better. That is how we are made in this country. We are not afraid to exchange the known and the existing for the new and innovative. If the opportunity is there, don't hesitate to take it.

That is precisely why there are already discussions about the next level in healthcare: personalised healthcare.

Health care for every person that is tailored to his needs.

Personalised healthcare gives us the opportunity to better understand the underlying causes of illness at the individual level and to translate these into treatments at the individual level. This is about precision and customisation.

As a result, medication and treatments will be many times more effective than they are now. This offers the prospect of serious savings in healthcare costs, because more precision prevents all kinds of unnecessary and costly overtreatment and undertreatment.

International experts in the field agree that personalised healthcare gives people around five extra years of life in good health.

The opportunities are there. So is joining forces.

Thanks to the revolution in Big Data & Artificial Intelligence, combined with the rapid development of biomedical science and related disciplines, we have everything we need to implement personalised care right now.

PHC-Catalyst was created to accelerate the transition towards this goal. We do this by forging a broad alliance of stakeholders from healthcare, government, science, business, politics, the pharmaceutical industry and patient associations.

Anyone who can contribute is welcome to join us. We have a unique opportunity to be one of the first countries in the world to make healthcare individually applicable. We can do this, so let's go for it.

To do together even better what we are already so good at.

Appendix 8: A concrete roadmap for value creation[xxxi]

What can individual health ecosystem actors already do to promote innovation and value creation in the health system?

In this article, we outline a concrete step-by-step plan that can already be applied to forming an ecosystem coalition around innovations in the Dutch health ecosystem.

Step 1: Define the target group and quantify the value you bring to them

- Define the characteristics of the desired target group
  - A target group can be, for example, a disease (diabetes), or a population segment (frail elderly over 85, low SES score with risk of chronic diseases), or a mix (people over 65 with diabetes and coronary complaints, 30-40 year old women with depressive complaints).

- Define the geographical scope (local, regional, national)

- Quantify the current situation of this target group
  - Prevalence, incidence, burden of disease (DALY), costs
  - Current cash flow, revenue pool and profit pool

- Determine the scope of the improvement for this segment
  - Which part of the care path/patient journey will be improved?

- Quantify the (relative) value of the improvement/innovation for that segment
  - Not the absolute/total value but the improvement compared to current alternatives
  - First in underlying drivers. For example: less time spent in hospital, fewer complications, etc.
  - Then translation into a measure of improved quality (e.g. QALY) and/or cost
  - In addition, the "non-care related" improvements, e.g. less absenteeism

Step 2: Determine who is paying and what they are willing to pay for this improvement

- Who is the payer (e.g. insurer, employer) and what is important to this party?

- To what extent is this payer willing to pay for the extra quality? If yes: quantify the payment per quality unit

- To what extent is the payer willing to share the efficiency improvement in the chain?

- Are there alternative payers? For example, the patients themselves? Who might be willing to pay for other things (e.g. productivity)?

Step 3: Determine the expected return on investment

- What are the investments needed to realise the improvement?

- What is (given the combination of points 1 and 2) the expected return? Is it balanced?
  This is initially a 'stand-alone' ROI for this particular intervention.
  Which is then supplemented with the ecosystem dynamics and distribution (see point 4)

Step 4: Determine the ecosystem coalition, and how there can be a 'net positive value' for each party

- Which ecosystem parties are crucial, which optional, which redundant?
  Find the right balance between scale and complexity: if a party is not necessary, do not let it be part of the coalition to reduce complexity.

- For the crucial parties: what is (without active redistribution) their benefit from the change and what are the drawbacks (costs, investments, complications, risks)?

- How do we improve that score so that all the necessary parties benefit from the innovation?
  Are there existing ecosystem parties outside this coalition that lose out?
  What will be their reaction, and should we mitigate that risk?

Note: from the perspective of an ecosystem party, steps 1 to 4 can be repeated several times for different combinations of focus target groups and improvements. If the same ecosystem coalition emerges each time, there is scale to be gained in cooperation.

Step 5: Set up the coalition with an explicit shared vision of value creation and value distribution

- Create a shared vision: what value do we create for the end customer/system?

- Scope of the cooperation: what do we do and do not do together, what are the roles and responsibilities?

- Value creation for the coalition: what do we expect as a total cash flow and profit pool?

- Return on investment for the individual coalition parties
  - What proportion of the above cash flow and profit pool does each party expect to receive
  - What investments does each party make? What costs and risks?
  - Sanity check: is this balanced within the coalition? This does not necessarily have to be done in each individual area of cooperation, as long as it is done at the portfolio level.

- Governance: how do we steer the coalition? Decision-making, meeting structure, reporting

- Concrete initiatives: deliverables, activities, milestone planning

Our greatest challenges are *value creation* and *value distribution*. Value creation by focusing on the combination of target groups and improvements that deliver the most value. Value distribution by introducing (and seeking) the right incentives in the system and forming effective coalitions with the right balance between scale and complexity. We hope that this publication can take all parties concerned a step further in this direction.

Appendix 9: Overview of PHC initiatives studied

Desk research Shining Towers - implementation barriers PHC							
Project name	Owner	Year	Description	Service	Succes?	Remarks	Type product/service
MammaPrint	NKI-AvL	2002	MammaPrint is the name of a molecular diagnostic test that can determine the risk of metastasis for non metastatic breast the risk of metastasis and can thereby help the physician in the choice of treatment (chemotherapy or not).	Landelijk beschikbaar	Yes	Is reimbursed by 90% of the health insurers from the additional package.	Behandeling / predictor
MijnIBDcoach	MUMC, Ferring, CCUVN en Sananet	2014	MyIBDcoach is a secure and personal page on the Internet designed for people with IBD. MyIBDcoach helps you to learn more about IBD and to learn what you can do yourself to keep your IBD under control. MyIBDcoach is also a help with treatment. Together with your MDL nurse / MDL doctor you manage the care plan. In this care plan, you keep a record of this progress. But also the agreements that are made about goals you would like to achieve are also recorded in the care plan.	Scale-up	Yes	The list of participating hospitals is growing (http://foundationmijnibdcoach.co.uk/doctors/), but there is no national coverage. MyIBDcoach started in 2014 with a trial, in which over 900 patients were included. The trial was completed in 2016. In 2016, several documents were drafted and submitted for publication.	Self-Management
DRUP studie	Centre for Personalised Cancer Treatment (CPCT) and Hartwig Medical Foundation	2016	The DRUP study provides out-of-treatment patients access to approved 'targeted' therapy based on the characteristics of their tumor cell, regardless of whether the therapy is approved for their indication.	Scale-up	Un-certain	Meanwhile, 40 hospitals are participating in the DRUP study. In the summer of 2017, the first results of the DRUP study were known: 38 percent of the first group of patients responded well to the treatment. But Hartwig MF is struggling to get the funding for the trials and is narrowing the indications.	Treatment / predictor
MediMapp	Sanofi en Soulve Innovations		MediMapp unburdens patients, by giving them grip on their own care process. MediMapp provides the right information at the right time and makes sure the patient is not overloaded with information. The app gives patients insight into their personal healthcare process, offers healthcare providers a total overview of the healthcare provided and enables digital interaction between both parties.	Scale-up	Yes	Originally developed for oncology, it is now also available for other indications including rheumatoid arthritis, MS and birth care. At this moment the Radboud UMC, Spaarne Hospital, Antoni van Leeuwenhoek, Bergman Clinics, LUMC and VieCuri are currently working with this app. The hospitals themselves pay for usage.	Self-Management
Ciro	Stichting Proteion Thuis en MUMC+	2010	Ciro is specialized in treating people with chronic lung diseases such as COPD and asthma, heart failure or sleep-related breathing disorders. The specialized treatments at Ciro are completely customized so that the complete program meets the needs of the patient.	Scale-up	Un-certain	Ciro collaborates with several hospitals so that patients can follow the tailor-made treatment program at a location nearby. The involved hospitals are; Maastricht UMC+, St. Jans Gasthuis (Weert), Elkerliek Hospital (Helmond), St. Anna Hospital (Geldrop), Laurentius Hospital (Roermond) and Catharina Hospital (Eindhoven).	Treatment
SanaCoach hartfalen en hartfalen/ COPD	"Hart+Vaat centrum MUMC+, Sananet	2007	This Sanacoach helps the patient to monitor their own health situation. The patient learns more about heart failure and learns how to control it. By means of periodic check-ups the SanaCoach asks the patient about the symptoms, limitations and problems. This makes it It is possible that the patient only needs to come to the consultation if it really makes sense.	Scale-up	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: MUMC+ Maastricht, OLVG, VieCurie, Maxima MC, Zuyderland MC.	Self-Management

Desk research Shining Towers - implementation barriers PHC							
Project name	Owner	Year	Description	Service	Succes?	Remarks	Type product/service
Oncology Data Network	IQVIA (CODE)	2017	The Oncology Data Network (ODN) is the first multi-country European collaboration of its kind revealing at scale how anti-cancer medicines are being used in near real-time. Our data-sharing network is open to all European cancer treatment centres and aims to inform best practice, highlight variations in care, accelerate research and help address financial sustainability challenges.	European		Helps oncology centers understand quality, innovation and value of care.	Community / data
Hartwacht	Luscii, Cardiologie Centrum Nederland (CCN) en ZKA	2018	Thanks to HartWacht, the cardiologists at CCN can monitor patients at home. This is done on a basis of measurements of, for example, weight and blood pressure and questionnaires which the patient fills out.	Nationwide available	Un-certain	Available to CCN patients only.	Monitoring / Self-management
EmmaCOPD	Medicine Men		PBM with the goal of intervening earlier with an (impending) COPD attack. Questionnaires, movement activity and sleep patterns and medication intake support are important indicators. Patient determines with which caregivers information is shared. Informal caregivers can be involved at an earlier stage, so that contact with care professionals can be prevented. Recent study by LUMC would show a 70% decrease in hospitalizations.				Self-management
SanaCoach COPD	Sananet	2008	The SanaCoach improves communication between between patient and caregiver and helps COPD patients to better monitor the health situation. People with COPD come to know more about their condition and learn to keep this chronic condition under control. Because of this greater involvement in (the treatment of) COPD, treatment results and quality of life increase for people with COPD.	Scale-up	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: MUMC+, Laurentius, OLVG, VieCurie, Maxima MC, Zuyderland MC.	Self-management
SanaCoach prostaatkanker	Sananet			Scale-up	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: Albert Schweitzer Hospital, Isala, Gelre, VieCuri.	Self-management
SanaCoach Parkinson	Sananet		The SanaCoach Parkinson's is an easily accessible program that is largely maintained by patients themselves maintained. It contains the following components: knowledge sessions, individual care plan periodic health check, monitoring module and preparatory consultation.	Pilot	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: Zuyderland MC.	Self-management
SanaCoach liesbreuk	Sananet		This SanaCoach is used for both pre- and post-operative guidance and monitoring of inguinal hernia patients. With an inguinal hernia there is a rupture in the groin. Since most patients recover smoothly from this procedure, a physical follow-up checkup is often unnecessary. Patients with complaints or complications, can be contacted for further follow-up at the hospital. The number of patients coming to the hospital for a check-up unnecessarily is reduced.	Pilot	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: Zuyderland MC.	Self-management

Desk research Shining Towers - implementation barriers PHC							
Project name	Owner	Year	Description	Service	Succes?	Remarks	Type product/service
SanaCoach MS	Sananet		The Sanacoach MS helps the patient to monitor their own health situation. He or she learns more about the disease and patients learn through self-management to better control the disease.	Pilot	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: Zuyderland MC, Academic MS Center.	Self-management
SanaCoach OSA (slaapapneu)	Sananet		The Sanacoach OSA helps people with sleep apnea to keep an eye on their own health under medical supervision, so that complications are prevented.	Pilot	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: St. Antonius.	Self-management
De Pijncoach	Sananet		This SanaCoach helps patients to monitor their own health status. Pain can be better monitored and improves the quality of life.	Scale-up	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: VieCuri, Zuyderland MC, Adelante rehabilitation center.	Self-management
Mijnbiological-coach	Sananet		With this SanaCoach, monitoring and registration takes place around the use of medication. Patients can ask questions via the message function in the SanaCoach and are thus guided online and remotely by healthcare providers.	Pilot	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: MUMC+.	Self-management
Mijnbreincoach	Sananet			Pilot	Un-certain	Sananet is a partner for a lot of eHealth apps. None of these apps are used nationwide. This app is used in the following hospitals: Alzheimer's Center Limburg.	Self-management
Drugtargetid	DTID	2016	We build molecular landscapes for complex genetic disorders to find novel diagnostic biomarkers and druggable targets within these landscapes. This leads to novel, disorder-specific and personalized genetic profiles, interventions and treatments. Furthermore, our landscapes considerably improve the understanding of the molecular basis of the disorders.	Pilot	Un-certain	DTID has started with a project through which the molecular landscape of Alzheimer's disease (AD) that we built will be extended and refined. In collaboration with the Department of Human Genetics, Radboud University Medical Center, The Netherlands, we will also try to validate the key putative drug target from our AD landscape in fruit flies (Drosophila). This project is funded by a Dutch foundation.	Diagnosis
MS Sherpa	Orikama data Science for Health	2016	A solution for and by people with Multiple Sclerosis. With a smart computer program we calculate how your MS behaves and develops. Because our software can learn, it is possible to recognize patterns in your data and, based on that, to be able to say more about the course of your condition. This makes therapy tailored to your needs, your needs, truly possible.	Pilot	Un-certain	A small group of people from the MS Society Nijmegen has been helping to test the app in daily practice for 3 years. Thanks to their input it is possible to create an app that helps to manage all the ups and downs of daily life with MS.	Self-management/ Predictor
Modhem			Researchers at Erasmus MC can characterise the blood diseases acute myeloid leukaemia and multiple myeloma in detail per patient. They do this using next-generation sequencing. This will enable them to improve diagnosis and prognosis, and will make treatment more efficient and personalised.	Pilot	Un-certain	The project by Valk and his colleagues focused on the implementation of NGS in the diagnostics of AML and MM at the department of Hematology at Erasmus MC, and sharing these results on a national and international level. In the case of AML, the implementation at Erasmus MC has been successful.	Diagnosis

Desk research Shining Towers - implementation barriers PHC							
Project name	Owner	Year	Description	Service	Succes?	Remarks	Type product/service
IQ healthcare	Radboudumc	2016	Together with RA patients and a multidisciplinary team of care providers, the e-health program called "Mastering Rheumatism Yourself" was developed. The program consists of a welcome module and 9 training courses. After going through the welcome module, the patient is given information about the training courses and fills out a questionnaire. Based on the answers he or she receives advice on the best course(s) to follow.	Pilot	Un-certain	In order to test whether "Tackling rheumatism by yourself" actually supports patients, the Radboudumc and the Sint Maartenskliniek is using an RCT to test whether patients have better self-management behavior after they have used the program.	Self-management
MS Community Panel	Ipsos	2018	The MS Patient Community Panel – which will run alongside Ipsos' MS Therapy Monitor – comprises 260 MS patients across the EU5 and US with a mix of treatment experiences. They will take part in a range of tasks throughout the year (both syndicated and proprietary), all moderated by Ipsos Healthcare's MS experts. This format will enable subscribers to explore key topics throughout the year, whilst also tapping into the community to answer business questions as they arise.	Pilot	Un-certain	Ook Ipsos NL doet mee. Nederland As patients move from recipients to participants, there is an imperative for pharma to put patients at the heart of current and future business models.Designed with this objective in mind, theMS Community will enable our clients to identify unmet patient needs, optimisetheirpatient communications, assess new ideas, and develop personalised medicine strategies for thoseliving with MS.	Community
Maastro	Maastro		Maastro is a nationally and internationally renowned radiotherapy center that explicitly wants to links between patient care, education and effective scientific research. Maastro uses prediction models with structural registration of treatment results.	Nationwide available	Un-certain	Maastro offers its services as a healthcare provider in Maastricht, Eindhoven, Liege, Hasselt and Aachen.	Treatment
HealthSuite	Philips		HealthSuite is supported by salesforce.com and is an open, cloud-based platform in which clinical and other data from various devices and sources are collected, correlated with each other and analyzed.	Nationwide available	Un-certain	Healthcare providers, chain partners and individuals have access to data relating to personal health, specific conditions of individual patients and entire populations. In this way, care can be better personalized and people gain more control over their own health, well-being and lifestyle.	EPD/data service
IHCH	International Health Centre The Hague		Actieve aanbieder van Genomic counseling, Pharmacy, Precision medicine (personalized medicine). Genomic counseling is an informative process whereby a person learns about their genome. Precision medicine, also termed personalized medicine, is a process used within the medical field that separates patients into different groups concerning medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. It will come to no surprise that your genes play a very important role in this.	Scale-up	Un-certain	Medical center with broad services where, among others, Dr. Philip Boerebach is actively involved in Genomic counseling, Pharmacy, Precision medicin.	Treatment
Niceday	Niceaday		App aimed at tracking progression/treatment of depression, anxiety and stress. Includes program, 1 on 1 counseling and tracks data. App is developed in collaboration with experts in the field.	Scale-up	Un-certain	Multiple organizations are now applying this. Among them Parnassia group.	Monitoring/ Self-management

Desk research Shining Towers - implementation barriers PHC							
Project name	Owner	Year	Description	Service	Succes?	Remarks	Type product/service
Brainclinics (vergelijkbare kliniek is neurocare-group.nl)	Brainclinics Research Institute		"Screening via EEG in people with ADHD and depression to predict effect of medication stimulation. See also: Personalized medicine in ADHD and depression: Use of pharmaco-EEG. Research Institute Brainclinics was founded in 2001 as an independent research institute, specialised in advancing the understanding of psychiatric disorders through brain imaging (QEEG, ERPs), chronobiology and sleep, Research Domain Criteria (RDoC), which knowledge should aid in a future of personalised medicine in mental health."	Scale-up	Un-certain		Predictor
Nutrikliniek	Nurtriclinic		HEALTHY LIVING BASED ON DNA AND LIFESTYLE. Clinic with test that provides information on genetic predisposition for obesity, diabetes, high blood pressure and elevated cholesterol.	Scale-up	Un-certain		Prevention
BreathBase Solution: SpiroNose (diagnostisch instrument) en BreathBase/ Cloud (analyseert input SpiroNose en koppelt/ vergelijkt input met data van longpatiënten)	Breathomix (founded in 2018)		"The innovative BreathBase Solution, including electronic nose (eNose) technology, analyzes the mixture of molecules in exhaled breath in real-time based on advanced signal processing and an extensive online reference database, infused with AI. Background info: The SpiroNose, an electronic nose' developed at the AMC can determine, on the basis of substances in the exhaled air which lung disease someone has. In nine out of ten cases, the device makes the correct diagnosis, research has shown. Breath data from 27,000 lung patients is collected and stored in BreathCloud which doctors can consult for making diagnoses. In the event of an inflammation, infection or lung tumour, the exhaled air contains specific substances that the SpiroNose detects within one minute. Research conducted in collaboration with the Netherlands Cancer Institute seems, moreover, that in lung cancer patients the device even before the start of treatment, can distinguish between patients who do or do not respond to immunotherapy. The expectation is that patients will be able to use the SpiroNose at their GP. The GP will be able to compare the breath data with the BreathCloud database, for a diagnosis and tailored medication. It can also detect lung cancer, COPD, asthma and diabetes."		Yes	"In the AMC and Radboud they are working with it. Is tested in 10 hospitals (including ALZ) for its application possibilities and reliability. CZ is working with CbusineZ (Rogier van der Hooft) to make this method + instruments widely available on a large scale.	diagnosis and predictor
Personal Health Train			The key concept in the PHT is to bring algorithms to the data where they happen to be, rather than bringing all data to a central place. The PHT is designed to give controlled access to heterogeneous data sources, while ensuring privacy protection and maximum engagement of individual patients and citizens. As a prerequisite, health data is made FAIR(Findable, Accessible, Interoperable and Reusable). Stations containing FAIR data may be controlled by individuals, (general) physicians, biobanks, hospitals and public or private data repositories.		Yes		Community

Desk research Shining Towers - implementation barriers PHC							
Project name	Owner	Year	Description	Service	Succes?	Remarks	Type product/service
Pacman	EIT health		The main objective of this project is to increase the number of patients who can be assigned to clinical trials with targeted drugs and to increase the number of patients for which response/resistance to targeted therapy is correctly predicted. Using tissues from the MOSCATO-01 trial, OncoSignal pathway analysis will be performed on tumour tissues without targetable mutation and treated targetable tumours, to validate that OncoSignal can identify more patients who will benefit from targeted therapy. Subsequently, further validation will be done by employing OncoSignal in prospectively running clinical studies at Gustave Roussy.				Predictor
U Prevent			provides tools for the individualisation of cardiovascular risk management on the basis of estimated individual risk and treatment effect.	Pilot			Preventie
farmaco-therapeutisch-kompas	Erasmus MC		The Department of Clinical Chemistry Erasmus MC is an International Centre of Excellence for Pharmacogenetics, and offers high quality tests for more than 20 enzymes. The tests are performed weekly: your result will be reported to your doctor within 2 weeks after receipt. A number of tests (DPYD, TPMT) are even reported within 1 week.	Nationwide available	Un-certain		
Farmaco-genetisch paspoort	UMCG						
My Tomorrows	My Tomorrows		myTomorrows provides information about and access to medicines that are still in the development phase or. for example, not (yet) registered in some countries. Access to these medicines can be regulated through clinical trials, expanded access and off-label use.	Scale-up			

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