TOWARDS A HIGH-PERFORMANCE ONCOLOGY RESEARCH SYSTEM

King Baudouin Foundation
Working together for a better society

COLOPHON

Title	**Towards a high-performance oncology research system**
	A publication of the King Baudouin Foundation rue Brederodestraat 21 B-1000 Brussels
Author(s)	Randy Mellaerts, *shiftN* Philippe Vandenbroeck, *shiftN*
Coordination King Baudouin Foundation	Gerrit Rauws, *Director* Isabelle Nguyen, *Independent Expert* Laurine Vanackere, *Project & Knowledge Manager*
Graphic design	Trinôme
	This publication can be downloaded free of charge from www.kbs-frb.be
Legal deposit	D/2893/2021/04
Order number	3763
	March 2021
	With the support of the (Belgian) National Lottery

TABLE OF CONTENTS

1 INTRODUCTION

The King Baudouin Foundation (KBF) manages a portfolio of over a hundred health research-oriented funds. Oncology research is an important component within that portfolio. The ambition of KBF is to support strategically chosen endeavors in the oncology research system with the intention to optimize patient value for cancer patients. Although KBF is a rather small actor in this field, they recently evolved towards a position of trusted convener, forum for stakeholder dialogue and actor of change. KBF wants to further explore this rather privileged position and take on such a connecting role to spur and support strategic collaborations.

Today, cancer is a significant challenge for society, healthcare systems and the growing number of affected patients and their families. A recent publication argued that new paradigms and conditions for responsible science and innovation policy across the European Union require (i) the collective action of Research & Development institutions, (ii) a system approach to health systems, higher education and patient organizations, and (iii) new initiatives to encourage international cooperation across an enlarged Europe; no single country can successfully fight the disease(s) on its own.[1] In Belgium we see that multiple actors (universities, knowledge institutes, patient organizations and for-profit organizations) are involved in oncology research as well.

The KBF contracted shiftN to support with a future-oriented, strategic reflection with a broad group of stakeholders with the aim to negotiate these friction points. The question put forward by KBF to guide the conversation was as follows: **'How can we ensure that cancer patients have rapid and affordable access to the results of evidence-based, publicly and philanthropically funded studies, to improve their life expectancy and quality of life?'** The group of stakeholders involved in this reflection represented key actors in the Belgian oncology research landscape, complemented with a number of international experts.

ShiftN set up a disciplined process of exploration (of contextual factors that orient the ecosystem) and design (of a high-performance oncology research model). The shiftN team was supported by a Guidance Committee[2] composed by KBF. The aims of the envisioned stakeholder consultation were therefore as follows: (i) to generate clear insights in the current oncology research system and a communicable problem definition, (ii) to facilitate the emergence of a shared vision on the design of an aspirational model of a high-performance oncology research system and (iii) to formulate a set of strategic recommendations endorsed by a broad stakeholder group. Another crucial point warrants attention: because of the uniqueness of existing partnerships and working methods in oncology research it may not be desirable to geographically limit the scope of the discussion to Belgium. Therefore, KBF seeks ways use the present initiative, with its geographically limited scope, as a launching pad for a more international effort that would involve key European and international actors.

1 https://febs.onlinelibrary.wiley.com/doi/abs/10.1002/1878-0261.12452

2 Guidance Committee: Lydie Meheus (Anticancer Fund), Frank Hulstaert (Belgian Health Care Knowledge Centre), Yannis Natsis (European Public Health Alliance), Jean-Benoît Burrion (Jules Bordet Institute)

2 METHODOLOGY

2.1 Approach

For the stakeholder consultation process a systems thinking approach was applied. This was operationalized based on a systems mapping methodology. Analytically the research team relied on two types of systems mapping, one of which is oriented towards understanding the bottlenecks in the current oncology research system (diagnostic strand), and another which aims to outline a model of a high-performance oncology research system (aspirational strand). Synthetic visualizations played an important role in structuring and guiding the stakeholder conversation. Systems thinking and dialogue are key elements of an approach to ground a social learning process around complex challenges[3]. The basic idea underpinning the research methodology is that a shared view of the complex interdependence of factors and bottlenecks that contribute to suboptimal patient value in the current oncology research system would pave the way towards a richer participatory effort to design a model of a high-performance oncology research system. Such collective understanding and design effort would subsequently lead to a more balanced and informed assessment of stakeholders of appropriate recommendations. Consultation of key stakeholders was pivotal to this research to better understand actors' basic assumptions and the values and norms in which they are embedded. Furthermore, active involvement of stakeholders in designing an aspirational model of a high-performance oncology research system and in the articulation of recommendations would likely increase their support for these actions and increase their viability. Finally, group-based processes of collective inquiry enhance the mutual understanding of worldviews in complex multi-stakeholder settings[4]. Figure 1 provides a schematic overview of the approach.

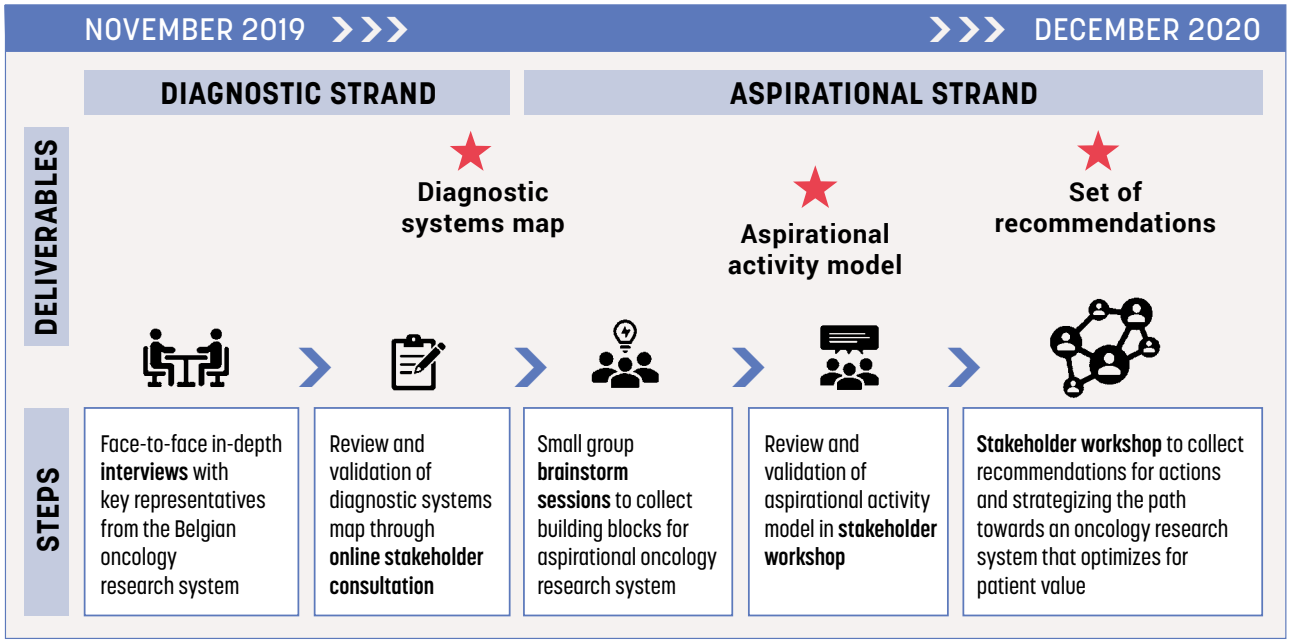


Figure 1: Schematic overview of the approach.

3 P. Vandenbroeck (2012) Working with Wicked Problems, King Baudouin Foundation, https://www.kbs-frb.be/en/Virtual-Library/2012/303257

4 V. A. Brown (2010) Collective Inquiry and Its Wicked Problems, in: V. A. Brown, J.A. Harris and J. Y. Russel, Tackling Wicked Problems. Through the Transdisciplinary Imagination, 61-83, Earthscan. London.

The research was conducted between November 2019 and October 2020 and structured as a sequence of the following steps[5]:

- Stakeholder consultation through face-to-face in-depth interviews with balanced sample of key representatives from the Belgian oncology research system;
- Synthesis of stakeholder views in a diagnostic systems map;
- Stakeholder review of the diagnostic systems map and articulation of building blocks for a high-performance oncology research system in a first online stakeholder consultation process;
- Small group sessions with stakeholders to collect building blocks for an aspirational model of a high-performance oncology research system;
- Design of an aspirational model of a high-performance oncology research system;
- Stakeholder review of the aspirational model of a high-performance oncology research system in a second workshop;
- Third stakeholder workshop to collect recommendations for actions and strategizing the path towards an oncology research system that optimizes for patient value;
- Writing of a summary report.

The research team of shiftN was supported by a Guidance Committee composed by KBF.

2.2 Systems Maps

Systems map is a generic label for a broad class of visual representations of complex systems or of the way they are perceived by human beings. By the notion of system, we understand 'a structured set of objects and/or attributes together with the relationships between them'. The constitutive elements of a system are, therefore, 1) its elements, 2) the relationships between these elements and 3) the system boundary that distinguishes between what does and does not belong to the set.

A systems map can take different forms. In this research we relied on a particular form of a so-called directed graph. A graph is in its most general sense a representation of a network, i.e. a set of nodes in which some pairs of the nodes are linked to one another. In a directed graph the connections have a direction associated to them (say, if there is a connection between node A and node B, then this connection will be denoted as being 'from A to B', or vice versa). Graphs can represent all kinds of networks.

In this research we relied on two distinct types of systems maps. Both are part of the broader class of directed network graphs. However, in this case they represent distinct conceptual logics. A diagnostic systems map was developed to visualize the factors that contributed to suboptimal patient value being generated by the Belgian oncology research system. The map reflects, in other words, why the system is not performing as well as it ideally should. A second map articulated an aspirational perspective in the form of a visual model of a patient-value guided oncology research system. The diagnostic map reflects a causal reasoning, linking suboptimal patient value to a variety of root causes; the aspirational model embodies a functional logic, showing interdependent sets of activities that jointly create patient value.

5 From March 2020 onwards, all stakeholder consultations and workshops took place via online platforms because of the COVID-19 pandemic.

Systems maps can serve different purposes:

- In general, as conceptual models, systems maps are used as tools for knowledge representation and learning. Their synthetic nature and streamlined syntax make them particularly suitable for showing 'the big picture'. This is particularly useful in dealing with complex challenges that spill over into different policy domains and scientific disciplines.

- As a result of their integrated, cross-disciplinary character, systems maps may become potent vehicles to support multi-stakeholder engagement and collaboration. A 'big picture' conceptual model provides a canvas for bringing different stakeholders together in focused and disciplined interactions. In this project the systems map was used to bring a variety of stakeholders together.

- The systems map was developed with the help of a web-based visualization platform (Kumu[6]). Each element of the systems maps can be documented with meta-data, turning the maps into portals to interactively explore a potentially extensive database. In this research project this was only a secondary objective given that the map was to a very large extent based on qualitative data collected via stakeholder interviews. Intentionally, this report does not include an inventory of the coded interview material, to make sure that opinions, quotes, and citations could not be attributed to interviewees. Protection of anonymity seemed a key requirement to maintain productive post-project stakeholder relationships.

- Systems maps are effective tools for the communication of important and complex messages throughout a decision-making process and particularly in the reporting and delivery phase. Customized versions of the systems maps can help to communicate the findings of the project to a broader audience. The present systems map offers that potential too.

6 https://kumu.io

2.3 Development of a diagnostic systems map

2.3.1 STRUCTURE AND STATUS OF THE DIAGNOSTIC SYSTEMS MAP

This systems map represents a network of drivers, or factors that contribute to suboptimal patient value.

The diagnostic systems map has been built inductively, based on 20 expert interviews. The map is not intended to present the one and only, final perspective on the Belgian oncology system as its scope and content reflects the limitations of the interview sample. But it was deemed robust enough to provide a solid foundation to support and frame a relevant strategic conversation about how more patient value and impact can be created with available public and philanthropic resources.

The syntax consists of just two elements: 'drivers' and 'links' between the drivers. The drivers and links are derived from statements made by stakeholders. The links between the concepts are understood as causal influences. So, a connection between drivers A and B is understood as 'A leading to B'. All drivers are expressed as variables locked in at a particular level. In other words, they reflect a judgment about the level of a system-relevant variable. For instance, the driver 'Lack of an integrated research strategy' reflects the perception that today the 'degree to which research strategy is integrated' is 'low'. Similarly 'unwillingness of hospitals to pass on patients' is a judgment about what the status is of the variable 'willingness of hospitals to pass on patients'. In this case, the assessment is that hospitals in the Belgian oncology research system are generally unwilling to pass on patients. In the interest of readability some of the drivers have been kept very short. E.g. 'Therapeutic freedom' would more expansively read 'The dominant ethos of therapeutic freedom in the medical profession'. The links denote 'leads to …'. For instance: '(A high level of) Patient-based financing of hospitals' leads to 'Unwillingness of hospitals to pass on patients'. 'Unwillingness of hospitals …' leads to 'Suboptimal treatment (of patients)'. In this research, all drivers eventually feed into 'suboptimal patient value' which is the central variable of the map.

2.3.2 SELECTION OF INTERVIEWEES

A longlist of stakeholders was drawn up capitalizing on the familiarity of KBS and the Guidance Committee with the oncology research arena. The longlist was reduced to a shortlist of 20 candidates through an iterative process between shiftN and the Guidance Committee. The shortlist sought to balance several criteria:

- Stakeholder type: Research institutes, funding organizations, governmental bodies, regulatory bodies and patient organizations.
- Region/language: The initial focus of this research is the Belgian oncology research system. Therefore, balance was sought between the francophone and Dutch-speaking interviewees.
- Geography: Because the Belgian oncology research system is embedded in a European and global context, a number of international experts were included. In addition, most of the Belgian representatives are recognized as international experts in the oncology research arena.

Altogether, these criteria sought to maximize representativeness in a rather heterogeneous stakeholder field composed of professional and sectorial subgroups. Eventually 20 interviews were conducted. One 'double interview' (with two interviewees) was included. The total number of people interviewed was 21. An overview is presented in Annex.

2.3.3 INTERVIEW GUIDE

The scope of the interviews had to match the objectives of the research phase, namely to understand why the current oncology research system leads to suboptimal patient value.

An interview guide was developed by shiftN and reviewed by the Guidance Committee. The interviews were semi-open and structured around a number of key questions. These were complemented with a list of subsidiary questions enabling the interviewers to tailor the conversation to individual interlocutors.

The list of key questions is as follows:

1. Can you describe the present oncology research system in your own words. Feel free to make a drawing.
2. Where do you see the main hurdles when moving from research ideas and outcomes to patients?
3. How would you define "patient-centric" and what is your view on measuring value for patients?
4. Which hurdles are being addressed by your mission/organization?
5. Where is (or who has) the leverage to address these hurdles? At the national level? At the European/global level?
6. Could you elucidate the enabling versus hampering role of intellectual property and data management?
7. What future trends or developments might make a significant difference in the challenge presented by these hurdles?
8. To what extent are these hurdles unique for oncology research?
9. How is oncology research in Belgium coupled with the European and Global level?
10. Take a white sheet of paper and make a drawing of functioning high-performance oncology research model. What are the (functional pieces) of such a model?
11. How could the currently available funding be used more efficiently in the context of patient benefits?
12. What would be a very desirable outcome of the present project?

Interviews were executed by 3 researchers from the shiftN team. The double interview was done by two interviewers together.

2.3.4 CODING OF INTERVIEWS

Interviews were fully transcribed by a single transcriber. The material was then coded by the 3 researchers from the shiftN team using dedicated qualitative research software. The methodology was based on the Collaborative Qualitative Analysis approach described by Richards et al. [7] This methodology enhances the trustworthiness underpinning the analysis process and maximizes consistency while working with more than one researcher-analyst for coding. Figure 2 presents an overview of the six steps involved in collaborative qualitative analysis.

Briefly, the six stages include (i) preliminary organization and planning, (ii) open and axial coding, (iii) development of a preliminary codebook, (iv) pilot testing the codebook, (v) final coding process, (vi) reviewing the codebook and finalizing the themes. The logic of this coding approach fits the scope of this research well as the systems map aimed to visualize stakeholders' perceptions on the dynamics of the current oncology research system and how it leads to suboptimal patient value.

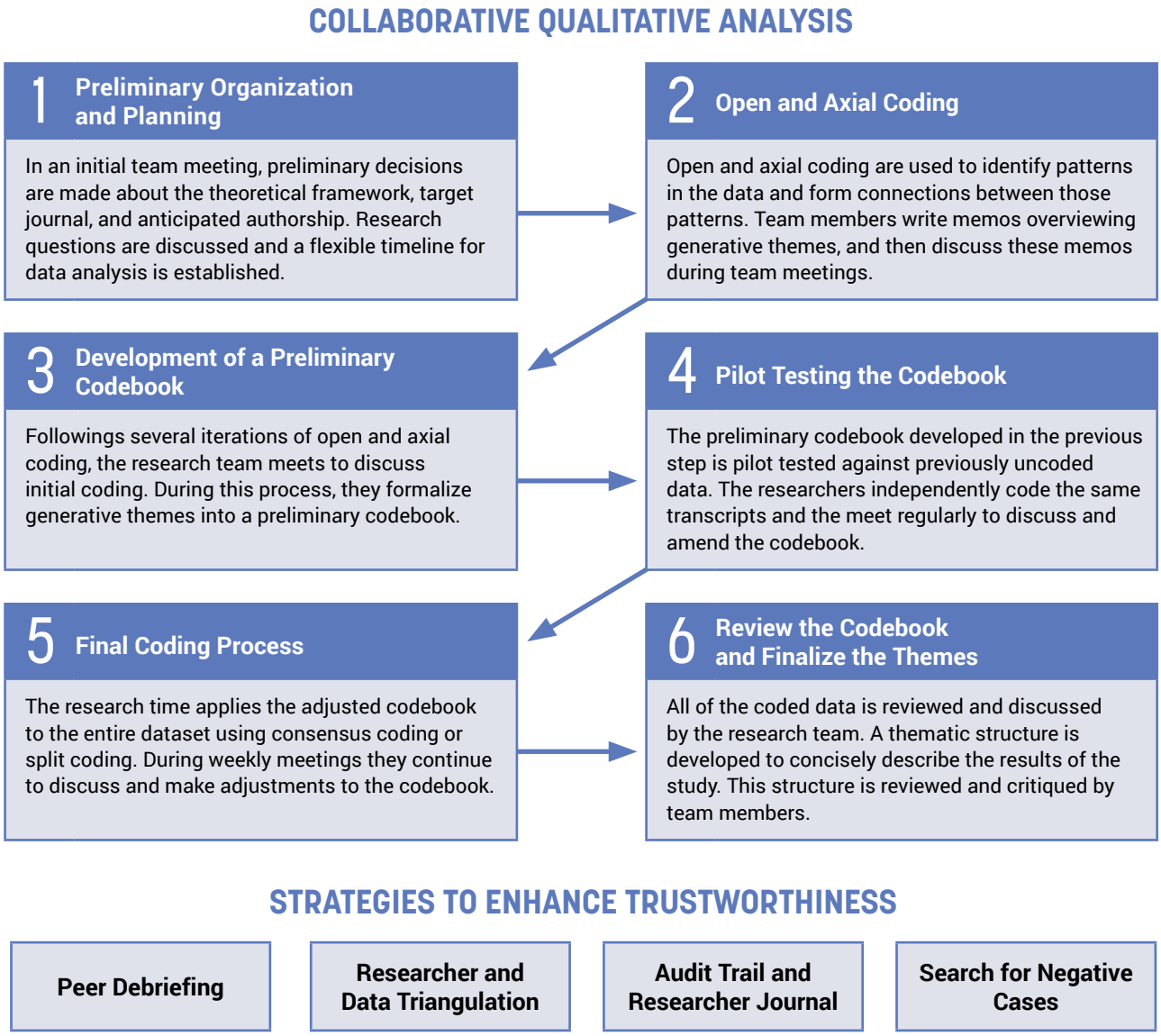


Figure 2: Overview of the six steps involved in collaborative qualitative analysis.

7 K. Richards et al. (2017) A Practical Guide to Collaborative Qualitative Data Analysis. Journal of Teaching in Physical Education 37(2):1-20.

2.3.5 STAKEHOLDER REVIEW OF THE DIAGNOSTIC SYSTEMS MAP

The coding of the interview material led to a preliminary version of the diagnostic systems map. The aim, status and architecture of the map were presented via an online webinar. The map was reviewed by the participants individually and feedback for improvement was collected via an online platform. A complete list of the participants can be found in Annex. The suggestions fell into different groups: additions of new drivers, addition of links between the drivers and suggestions to rephrase several drivers for the sake of clarity. So, these suggestions mainly had a bearing on the micro-and meso-level architecture of the map. The overall structure was not put into question. The suggestions were processed by the shiftN team, which led to a more evolved version of the diagnostic systems map. This version was used as input to small group sessions with stakeholders to collect building blocks for an aspirational model of a high-performance oncology research system.

2.4 Development of an aspirational model of a high-performance oncology research system

2.4.1 STATUS OF THE ACTIVITY MODEL

The aspirational model of a high-performance oncology research system was built using the syntax of an activity model[8]. An activity model looks superficially similar to the diagnostic systems map described in the previous section. However, the underlying logic is very different. An activity model is a model of purposeful activity. Its basic elements are activities, and the model shows the logical interdependence of these activities to realize a particular purpose. In the context of this stakeholder trajectory, the purpose of a high-performance oncology research model is to optimize patient value.

2.4.2 USE OF THE ACTIVITY MODEL

The activity model developed in this stakeholder trajectory serves multiple purposes:

- It is a powerful aid to conduct a gap analysis and for strategizing. Because we can use this aspirational model to conduct a gap analysis with the existing situation as it is perceived by stakeholders. For each activity we can ask: does it exist in the real world? Who takes care of it? In general: who contributes to what? How are activities implemented and how is their performance assessed? Who is responsible for relaying between activities? These reflections will point to functional and organizational gaps in existing systems, and to inefficiencies and overlaps that can be eliminated.
- The activity model embodies aspirations of a wide range of stakeholders. This implies that it serves as a boundary subject for alignment and envisioning a shared vision on a high-performance oncology research system.

8 P. Checkland, J. Poulter (2006) Learning for Action. A Short Definitive Account of Soft Systems Methodology, and its use for Practitioners, Teachers and Students. Wiley. Chichester.

- The activity model is also used in tandem with the diagnostic systems map. The difference in logics underling both maps allow stakeholders to come to grips with the challenges in the current system and strategizing their way towards the aspirational model of a high-performance oncology research model.

2.4.3 PARTICIPATORY DESIGN OF THE ACTIVITY MODEL

Based on the insights and 'big picture' provided by the diagnostic systems map, stakeholders were invited to articulate suggestions for a high-performance oncology research system during a series of 3 small group discussions. This input was used to draft a preliminary activity model which was reviewed by the Guidance Committee. Hereafter, the shiftN team designed a first version of the activity model based on the suggestions provided by the stakeholders and the Guidance Committee. This first version of the activity model was presented in an online workshop and participants were invited to share their general reflections in a plenary session and their suggestions for improvement in several subgroups. This feedback was the basis for a final iteration and resulted into the final version of the activity model. Lists of participants for all the stages can be found in annex. The designed activity model embodies the aspirations of stakeholders for a high-performance oncology research system. The participatory design resulted in a vision shared by the stakeholders involved in the process.

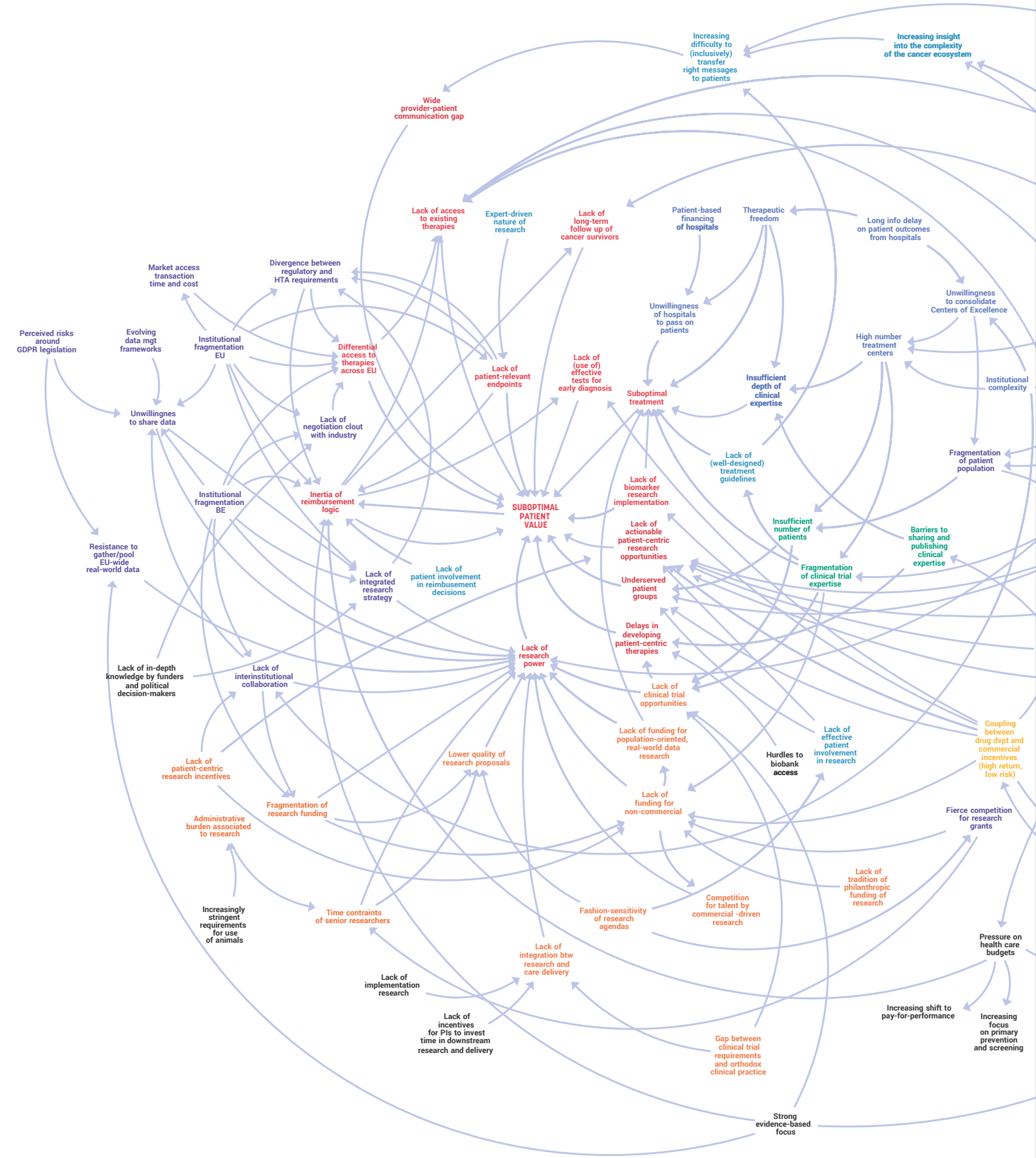
2.5 Recommendations

2.5.1 STAKEHOLDER DELIBERATION ON RECOMMENDATIONS FOR A HIGH-PERFORMANCE ONCOLOGY RESEARCH SYSTEM

A third and final online workshop was organized to collect recommendations for actions and strategizing the path towards an oncology research system that optimizes patient value. The final version of the activity model was used as a starting point. This model represents a gap with the existing system and the assignment for the participants was to assess this gap and formulate recommendations for closing it. Practically, the participants were divided into several smaller subgroups and were requested to formulate up to 5 recommendations. They also were asked to provide a rationale for each recommendation by answering the following questions:

- What action can we take now to move towards our aspirational high-performance oncology research system?
- How does the recommendation connect with the current system and how does it align with the aspirational model?
- What actor constellation will be needed to drive this action forward?
- Who can be the ambassador or champion of the action when moving forward?
- What are critical factors for this action to result in the desired outcome?

This enabled us to harvest recommendations from a wide range of stakeholders. The list of participants can be found in annex. At this point, KBF and researchers from the shiftN team do not pronounce themselves on the feasibility and desirability of changes. Stakeholders may have different positions on that.


Increasing difficulty to (inclusively) transfer right messages to patients
Increasing insight into the complexity of the cancer ecosystem
Wide provider-patient communication gap
Lack of access to existing therapies
Expert-driven nature of research
Lack of long-term follow up of cancer survivors
Patient-based financing of hospitals
Therapeutic freedom
Long info delay on patient outcomes from hospitals
Market access transaction time and cost
Divergence between regulatory and HTA requirements
Unwillingness of hospitals to pass on patients
Unwillingness to consolidate Centers of Excellence
Perceived risks around GDPR legislation
Evolving data mgt frameworks
Institutional fragmentation EU
Differential access to therapies across EU
Lack of patient-relevant endpoints
Lack of (use of) effective tests for early diagnosis
High number treatment centers
Suboptimal treatment
Insufficient depth of clinical expertise
Institutional complexity
Unwillingnes to share data
Lack of negotiation clout with industry
Lack of (well-designed) treatment guidelines
Fragmentation of patient population
Lack of biomarker research implementation
Institutional fragmentation BE
Inertia of reimbursement logic
SUBOPTIMAL PATIENT VALUE
Insufficient number of patients
Barriers to sharing and publishing clinical expertise
Lack of actionable patient-centric research opportunities
Resistance to gather/pool EU-wide real-world data
Lack of integrated research strategy
Lack of patient involvement in reimbusement decisions
Fragmentation of clinical trial expertise
Underserved patient groups
Delays in developing patient-centric therapies
Lack of research power
Lack of in-depth knowledge by funders and political decision-makers
Lack of interinstitutional collaboration
Lack of clinical trial opportunities
Coupling between drug dvpt and commercial incentives (high return, low risk)
Lack of funding for population-oriented, real-world data research
Lack of effective patient involvement in research
Hurdles to biobank access
Lack of patient-centric research incentives
Lower quality of research proposals
Fragmentation of research funding
Lack of funding for non-commercial
Fierce competition for research grants
Administrative burden associated to research
Lack of tradition of philanthropic funding of research
Increasingly stringent requirements for use of animals
Time contraints of senior researchers
Competition for talent by commercial -driven research
Fashion-sensitivity of research agendas
Pressure on health care budgets
Lack of integration btw research and care delivery
Lack of implementation research
Increasing shift to pay-for-performance
Increasing focus on primary prevention and screening
Lack of incentives for PIs to invest time in downstream research and delivery
Gap between clinical trial requirements and orthodox clinical practice
Strong evidence-based focus

3 RESULTS

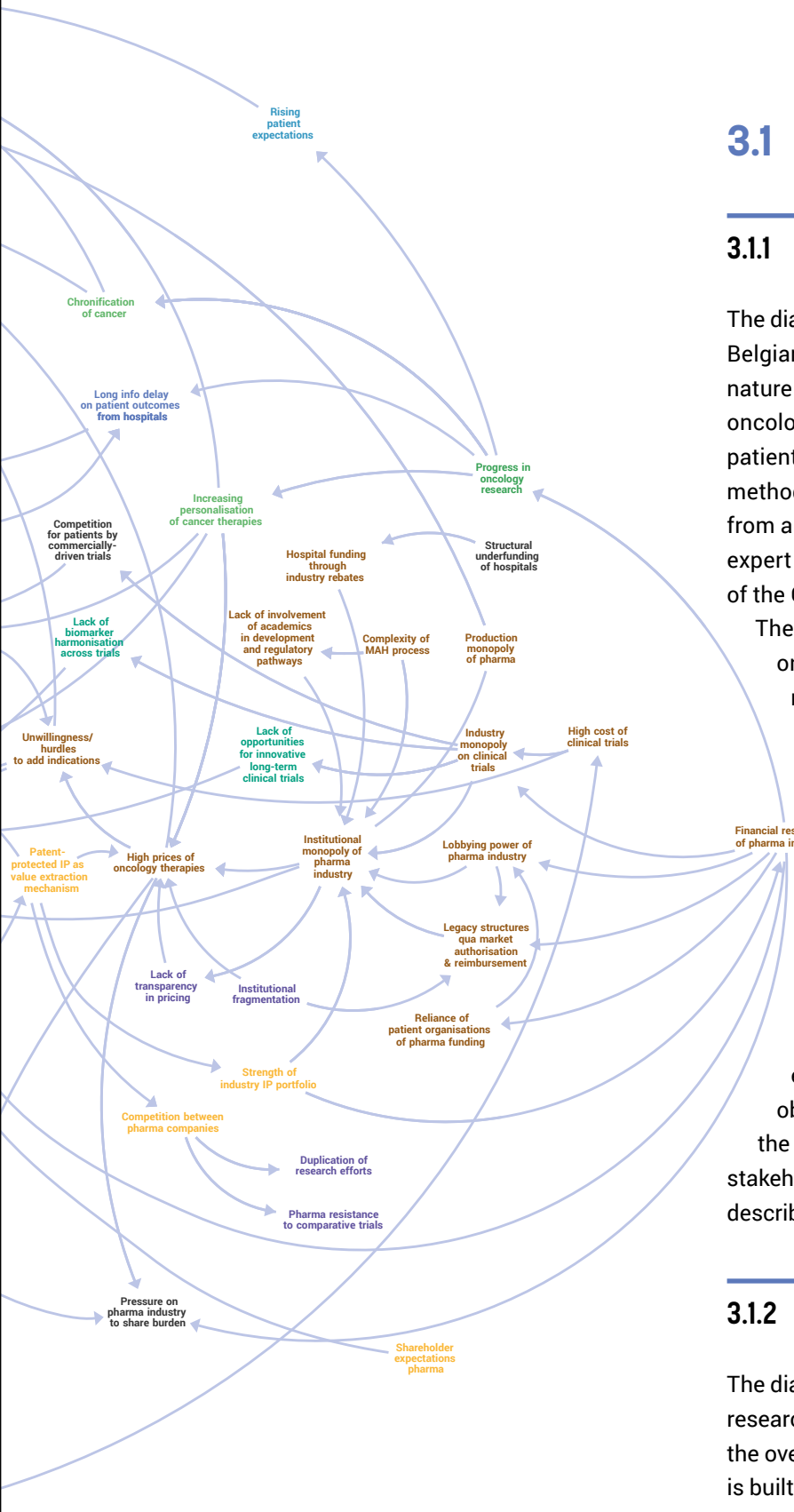


Figure 3: The diagnostic systems map of the Belgian oncology research system.

3.1 Diagnostic systems map

3.1.1 AIM AND STATUS OF THE MAP

The diagnostic systems map provides a picture of the Belgian oncology research system. It is diagnostic in nature meaning that it aims to show why the Belgian oncology research system is not creating as much patient value as we might expect. As mentioned in the methodology section, the map has been developed from a limited set of qualitative data, i.e. twenty expert interviews. Also, the views from the members of the Guidance Committee have been considered.

The map is not intended to present the one and only, final perspective on the Belgian oncology research system. Its aim was to support and frame the strategic reflection about how more patient value can be created with available public and philanthropic resources.

To summarize: throughout this work, the diagnostic systems map's function is two-fold. Firstly, its analytic function it to provide us with a bird's eye overview of why the Belgian oncology research system is not creating as much patient value as we might expect. And secondly, it served as a 'boundary object' to facilitate a common understanding of the current oncology research system on which stakeholders could formulate improvements. This is described in the next section.

3.1.2 ARCHITECTURE OF THE MAP

The diagnostic systems map of the Belgian oncology research system is presented in Figure 3. In line with the overall ambition of the research project, the map is built around a nodal element: 'suboptimal patient value'. In this way the map helps to explain why suboptimal value exists in the system. Many links converge on this nodal element.

First degree drivers

The first-degree drivers are the elements that connect directly to the nodal element. Figure 4 provides a detail of the diagnostic systems map with the following 13 first-degree drivers (clockwise):

1. Lack of patient-relevant endpoints
2. Lack of long-term follow-up of cancer survivors
3. Lack of effective tests for early diagnosis
4. Suboptimal treatment
5. Lack of biomarker research implementation
6. Lack of actionable patient-centric research opportunities
7. Underserved patient groups
8. Delays in patient-centric therapies
9. Lack of research power
10. Inertia of reimbursement logic
11. Differential access to therapies across EU
12. Widening provider-patient communication gap
13. Lack of access to existing therapies

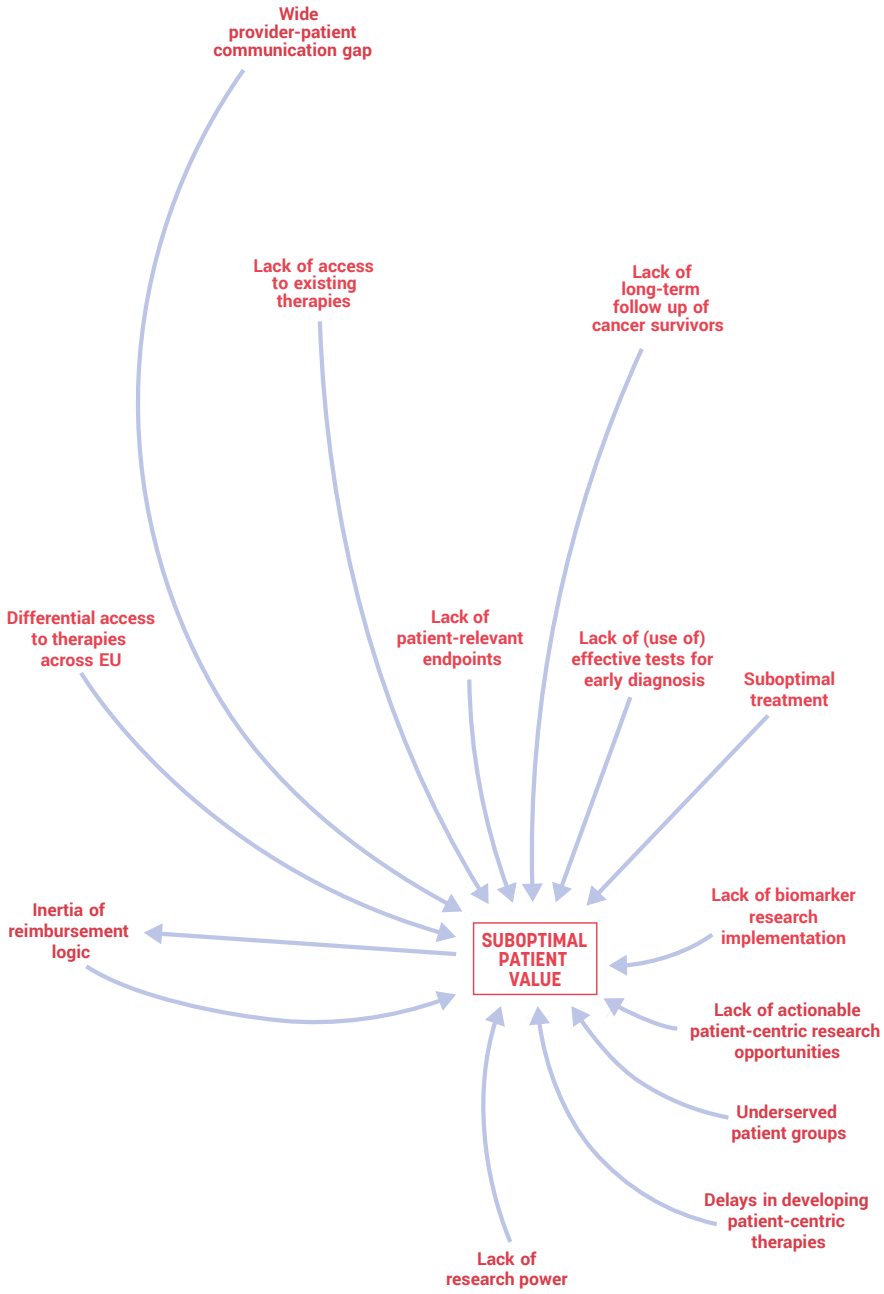


Figure 4: Detail of the nodal element 'suboptimal patient value' in the diagnostic systems map and its first-degree drivers.

Description of clusters of the diagnostic systems map

The first-degree drivers are connected with second-degree drivers and further onwards. The map can be divided into thematic clusters grouping the drivers. The 9 thematic clusters are:

1. Institutional fragmentation
2. Challenges in non-commercial research
3. Pharma business model
4. Pharma institutional monopoly
5. Challenges in clinical trials
6. Dynamics between treatment centers in Belgium
7. Scientific progress
8. Communication with patients
9. Patient involvement

1. Institutional fragmentation

The fragmentation of the oncology research landscape features as a factor at Belgian and at EU level. It has numerous downstream implications:

- As a result of the fragmentation all actors in the ecosystem struggle with a lack of interinstitutional collaboration; the absence of an integrated research agenda; and an unwillingness to share data. These factors undermine the effectiveness of oncological research efforts ('lack of research power');
- For payers the fragmentation results in 'lack of negotiation clout with industry';
- For industry the fragmentation results in unwanted 'market access transaction time and costs';
- For citizens the fragmentation results in a 'differential access to therapies across the EU'. Also the 'divergence between regulatory and HTA requirements' feeds into the 'lack of patient-relevant end points' which is an obvious impediment to realizing patient value.

Figure 5 presents a detail of the cluster institutional fragmentation.

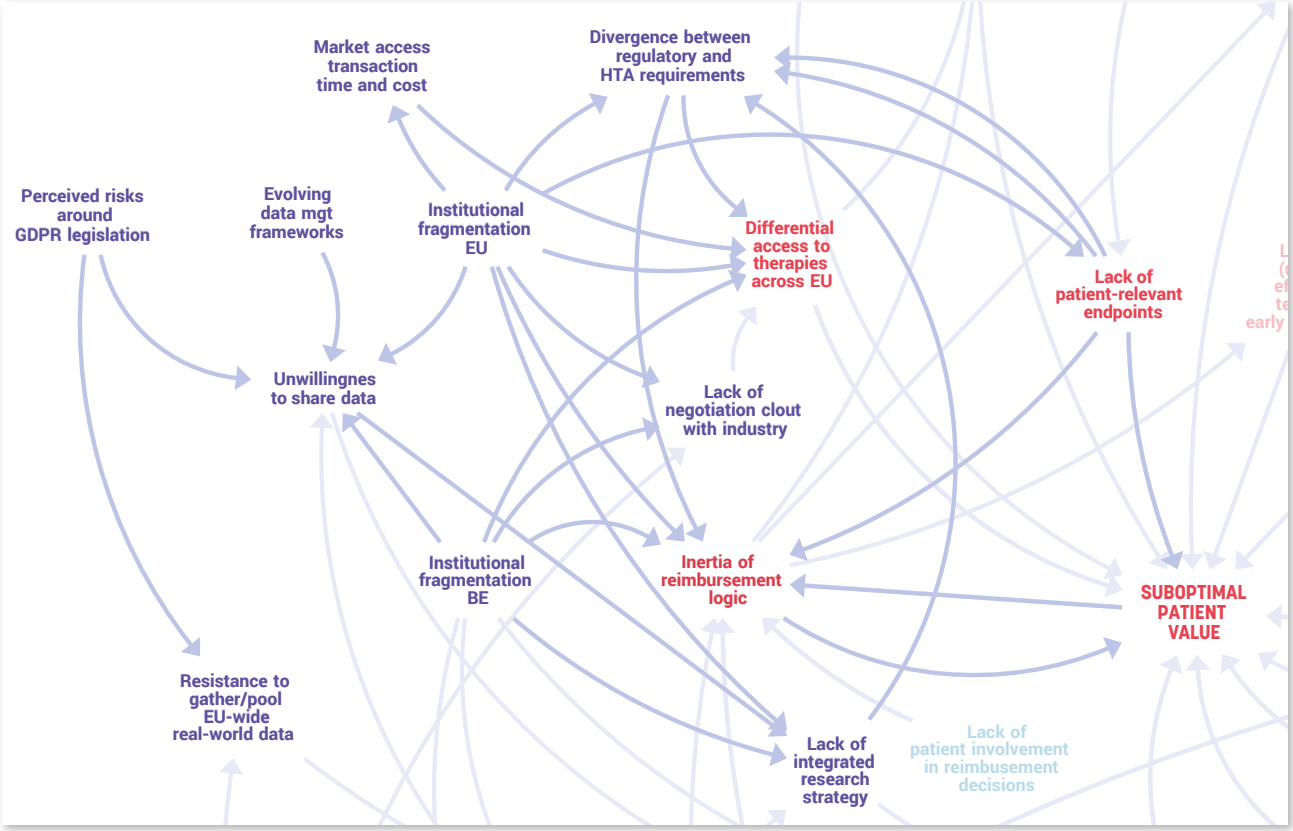


Figure 5: Detail of the cluster institutional fragmentation.

2. Challenges in non-commercial research

Figure 6 presents a detail of the challenges that are particularly related to non-commercial environments. These include research settings that are mainly funded through public and philanthropic resources. Many of the links in this cluster converge on 'lack of research power' as first-degree driver of 'suboptimal patient value'. This means that the investment in research resources does not yield what it might be able to achieve. In other words, there is some leakage in the system in terms of quality, speed, and effectiveness of the research. These research efforts are typically not integrated or coordinated with industry sponsored research, adding to the inefficiency.

Many drivers in this cluster are feeding into 'lack of research power'. Some of them are quite operational such as 'administrative burden associated to research' and 'time constraints of senior researchers'. More fundamental drivers are related to funding such as 'fragmentation of research funding' and 'lack of funding for non-commercial research'. Another important driver in this cluster is 'lack of clinical trial opportunities' and this driver is mainly fed by elements in the cluster of 'challenges in clinical trials' such as 'insufficient number of patients' and 'fragmentation of clinical trial expertise'.

Finally, on the left-hand side of the cluster, the driver related to 'lack of patient-centric research incentives' refers to the fact that in non-commercial sphere there is no economic incentive to engage in patient-centric research. And this feeds into the 'lack of institutional collaboration' that is at the heart of the first cluster.

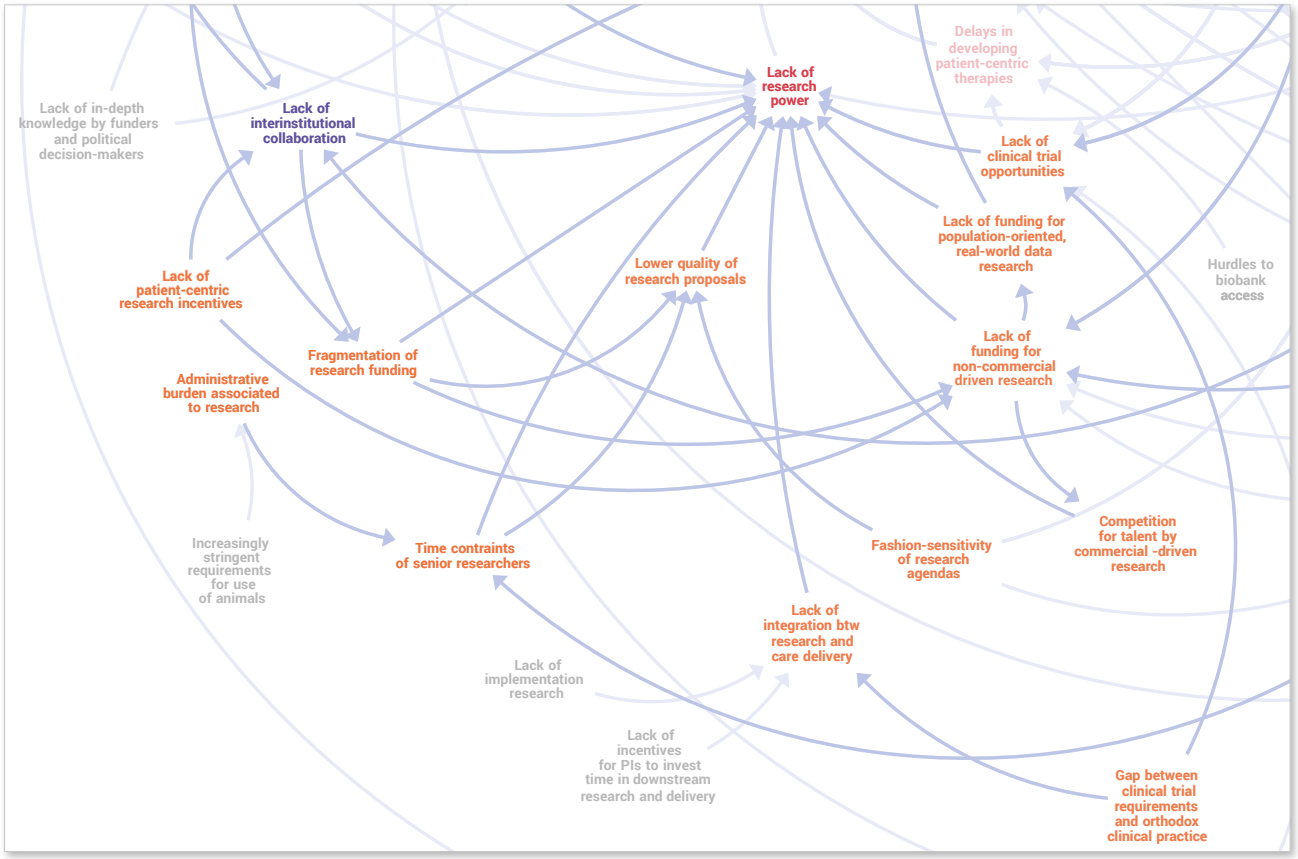


Figure 6: Detail of the cluster challenges in non-commercial research.

3. Pharma business model

The cluster 'pharma business model' is built around two key drivers: 'patent-protected IP as value extraction mechanism' and 'coupling between drug development and commercial incentives (high return, low risk)'. The latter connects to several first-degree drivers such as for example the 'lack of actionable patient centric research opportunities' (cfr. Figure 7). This is an important link meaning that there is a gap between what commercial imperatives dictate companies to do and what patients really need.

4. Pharma institutional monopoly

The pharma industry drives the logic of oncological research in a substantial way. That is why it has an institutional monopoly. This is driven by its access to vast financial resources, its lobbying power and unfettered access to regulators, its capacity to influence other actors (patient organizations, hospitals), its production monopoly, and its de facto monopoly on clinical trials. A detail of the cluster with corresponding drivers is displayed in Figure 8. This gives the industry a lot of leverage in price setting ('high prices of oncology therapies'). Also, this position limits the potential of actionable patient-centric research opportunities.

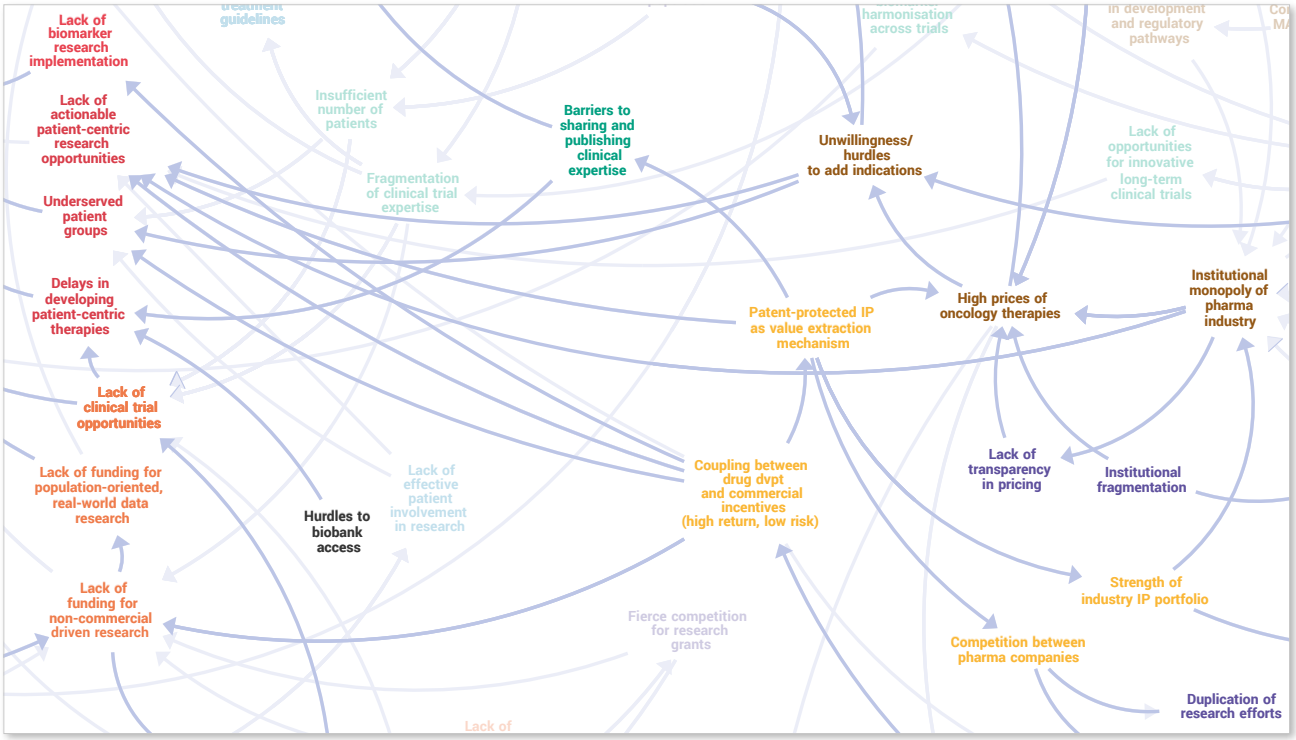


Figure 7: Detail of the cluster pharma business model.

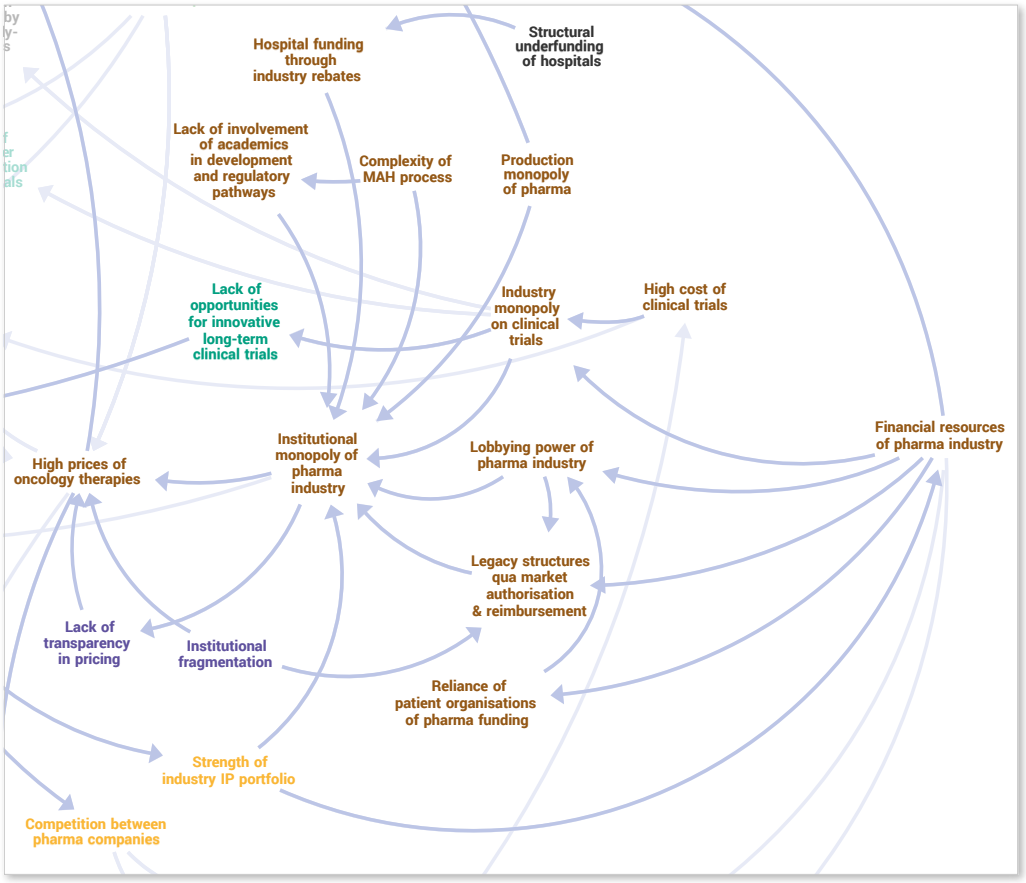


Figure 8: Detail of the cluster pharma institutional monopoly.

5. Challenges in clinical trials

The cluster is presented in Figure 9 and it takes form as an axis that cuts horizontally through the map. Starting from 'progress in oncology research', to 'increasing personalization[9] of cancer therapies', down to 'fragmentation of patient population', 'insufficient number of patients', 'fragmentation of clinical trial expertise', eventually leading to 'lack of clinical trial opportunities'. Important sequence of drivers to acknowledge in the map. The 'fragmentation of patient population' is also closely linked to the cluster on top of that, which is 'dynamics between treatment centers' in Belgium.

The core drivers here relate to manifestations of fragmentation, notably of clinical trial expertise and of patient populations that are involved in trials. There are institutional and scientific drivers behind this fragmentation. 'Progress in oncology research' leads to 'increasing personalization of cancer therapies', which limits the size of patient populations that can participate in a trial. Additionally, typical for Belgium is the 'high number of treatment centers'. This is a factor that contributes to fragmentation of expertise and populations. There are other challenges related to clinical trials, notably the 'lack of opportunities for innovative long-term trials' (which is itself rooted in the industry monopoly on clinical trials) and the 'lack of biomarker harmonization across trials' which undermines the effectiveness of research ('lack of research power') and negatively impacts the later implementation of targeted therapies in routine care.

9 *Post scriptum:* A recent report of Gill et al. elaborates on the terminology of 'personalized', 'precision' and 'stratified'. The driver 'increasing personalization of cancer therapies' encompasses all three dimensions. Jennifer Gill; Anna-Maria Fontrier; Aurelio Miracolo and Panos Kanavos (November 2020) 'Access to Personalised Oncology in Europe' London School of Economics https://doi.org/10.21953/5zsbeehvd3u8

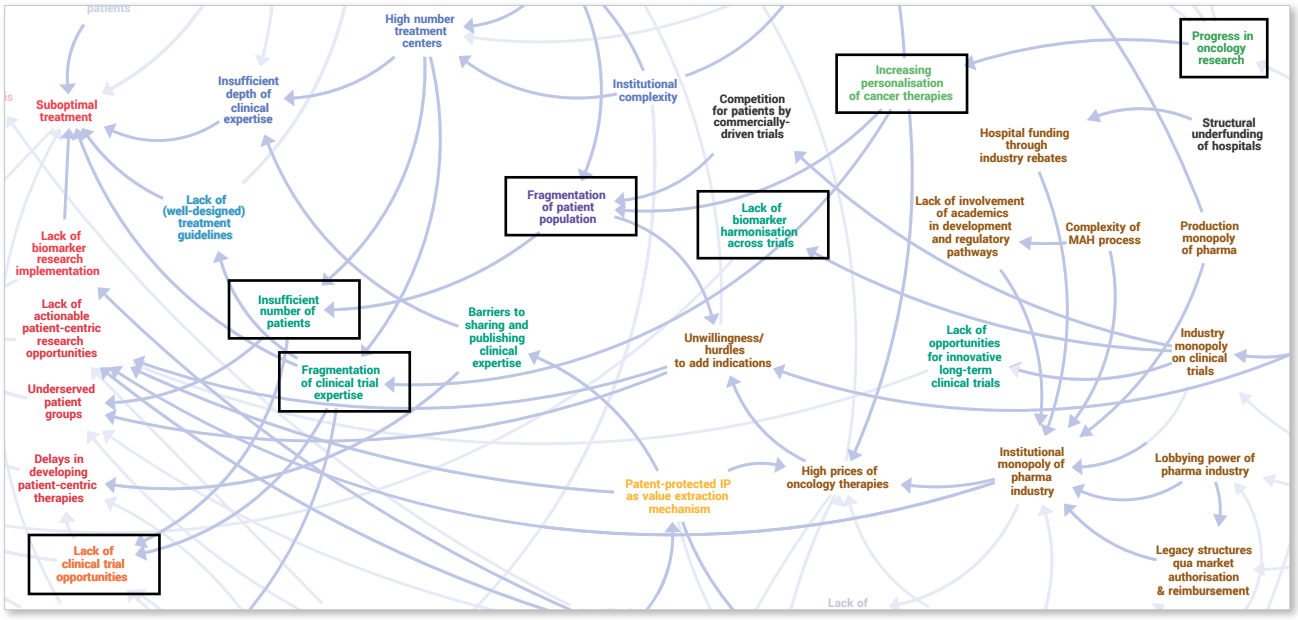


Figure 9: Detail of the cluster challenges in clinical trials.

6. Dynamics between treatment centers in Belgium

This cluster depicted in Figure 10 pivots around the 'high number of treatment centers' in Belgium which leads to both fragmentation and 'insufficient depth of clinical expertise'. The existence of these high numbers of treatment centers is explained by political and cultural factors including an 'unwillingness to consolidate centers of excellence', 'institutional complexity' and the 'long info delay on patient outcomes from hospitals'. Treatment centers are generally also unwilling to pass on patients to one another, to an important extent a result of the financing logic in the Belgian healthcare system. The income of hospitals in Belgium depends to some extent (a few percentages) on the discounts obtained on expensive and reimbursed medicinal products and medical devices. Such incentive may not always encourage the practice of evidence-based medicine. Many of these drivers feed into the first-degree driver 'suboptimal treatment' of patients, which is an obvious impediment to generating patient value.

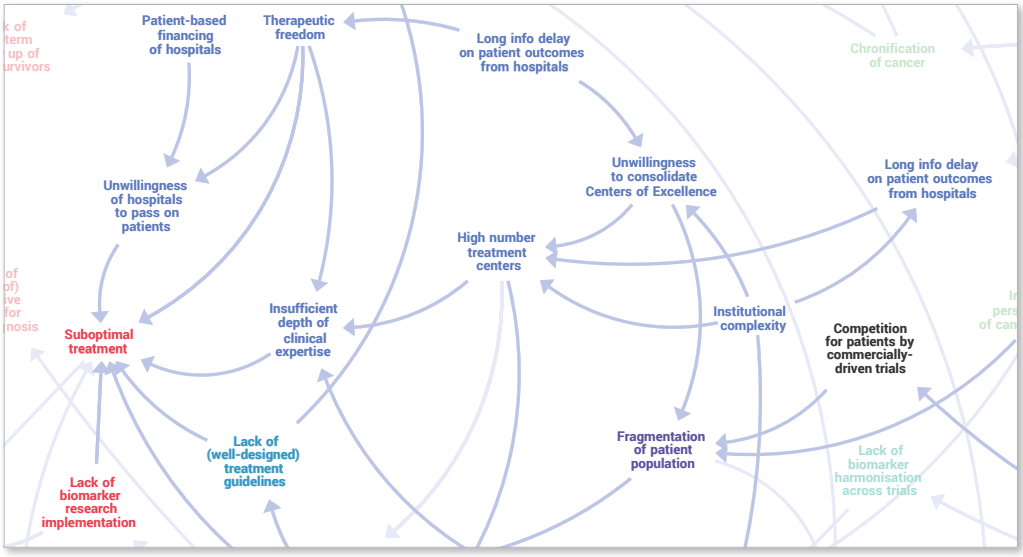


Figure 10: Detail of the cluster dynamics between treatment centers in Belgium.

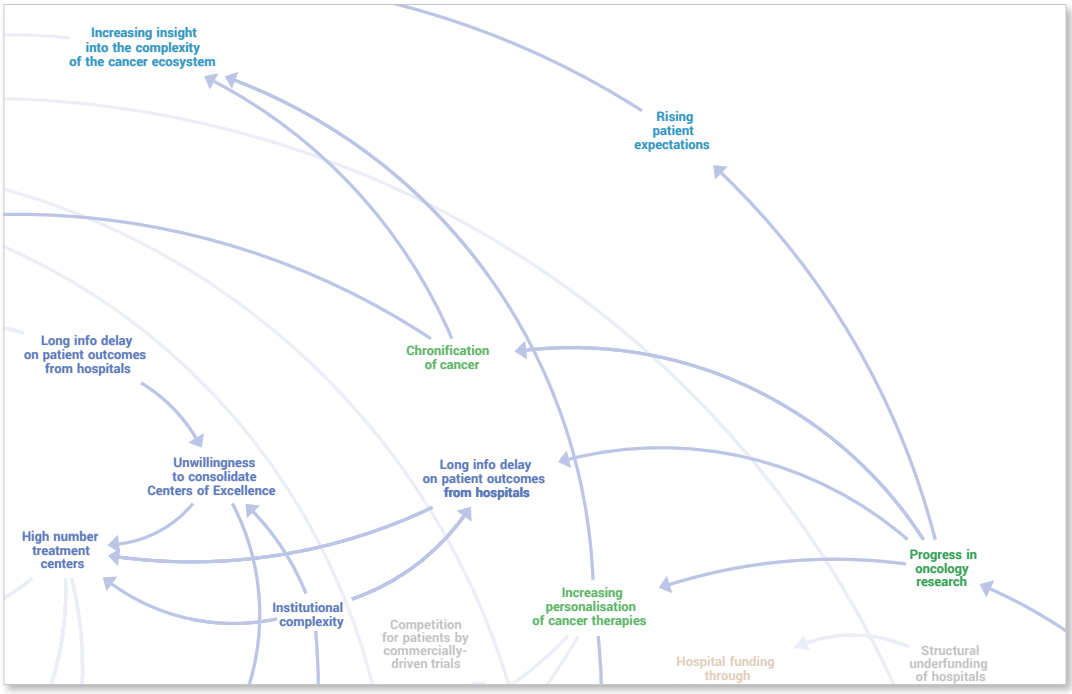


Figure 11: Detail of the cluster scientific progress.

7. Scientific progress

This cluster is linked to scientific 'progress in oncology research'. Figure 11 displays three other elements, namely 'increasing personalization of cancer therapies' that feeds into the clinical trial cluster, 'rising patient expectations' that feeds into the cluster 'communication with patients', and 'chronification of cancer'.

8. Communication with patients

This cluster communication with patients is displayed in Figure 12 and hinges on the perceived 'increasing difficulty to (inclusively) transfer the right messages to patients'. This goes back to a number of factors: the 'lack of well-designed treatment guidelines', 'rising patient expectations', and the 'increasing insight into the complexity of the cancer ecosystem' (which in itself goes back to increasing personalization of treatment and chronification of the pathology). Eventually this leads to the central element 'suboptimal patient value' through the 'wide provider-patient communication gap'.

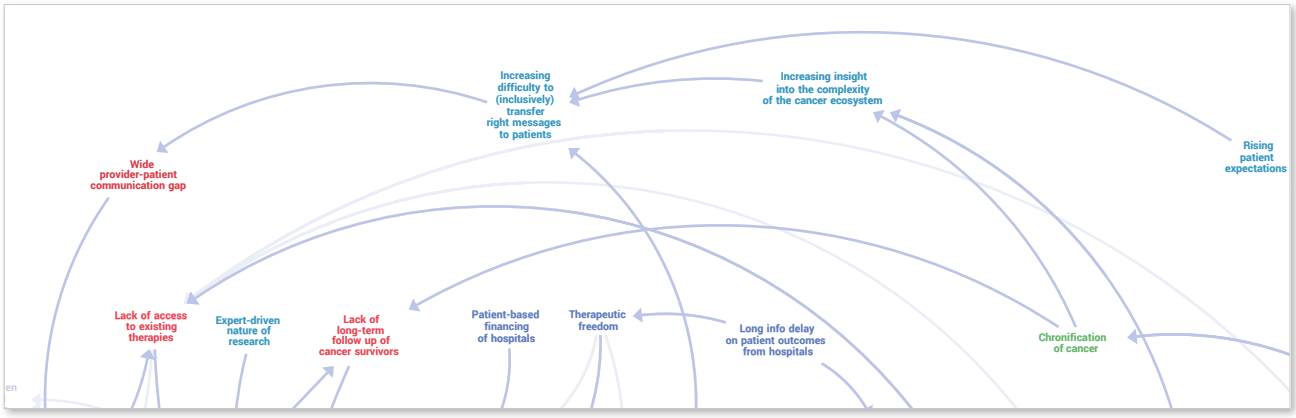


Figure 12: Detail of the cluster communication with patients.

9. Patient involvement

The final cluster is dispersed into the system map as a combination of three different elements which refer to insufficient or lack of involvement of patients in various key functions of the research system. Both in terms of dictating the scope and direction of the oncology research ('lack of effective patient involvement in research', 'expert-driven nature of research', 'lack of patient-relevant endpoints) as well as in reimbursement decisions. The elements are presented in Figure 13.

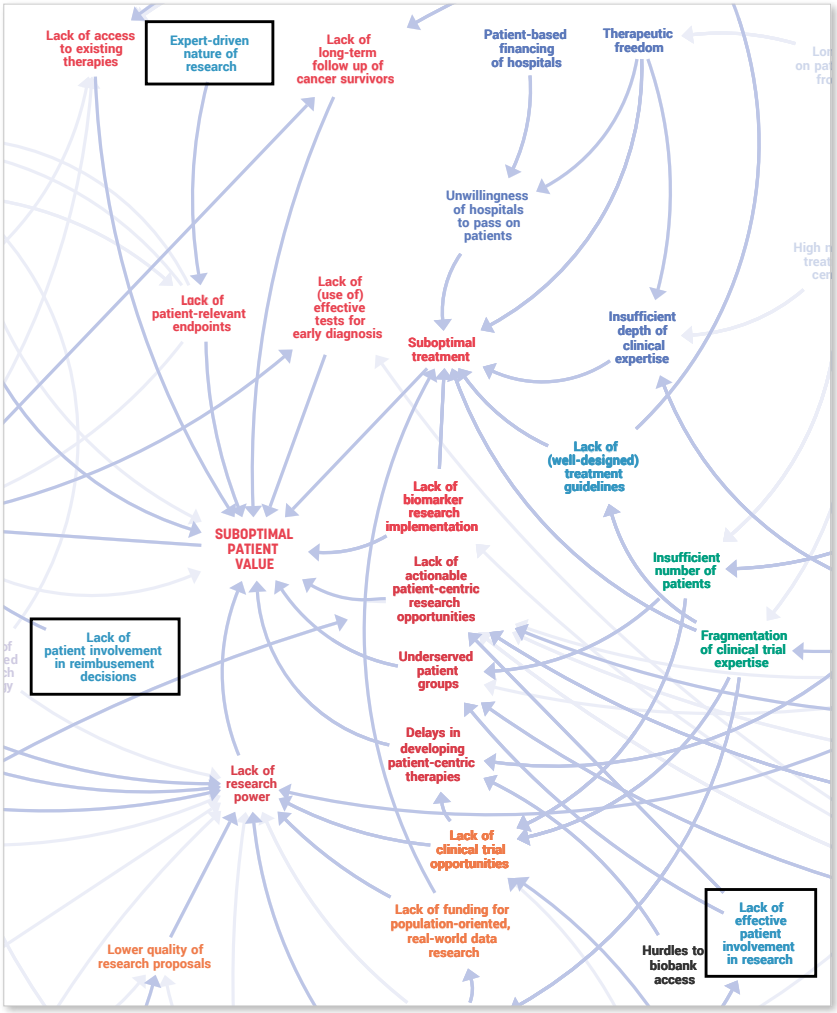


Figure 13: Detail of the cluster patient involvement.

3.1.3 SUMMARY

The diagnostic systems map shows that the perceived lack of patient value is the result of the interaction between many factors. They range from the very operational to the very strategic and span the whole ecosystem of actors (industry and their shareholders, academia, patients, funders, regulators, payers). The map reflects that it is conceptually not possible to consider the oncology research system funded by public and philanthropic resources as separate from an industry-funded research system. They interact with one another in myriads of ways. Based on this map one can argue that the oncology research system as a whole is not well equipped to generate patient value. Fragmentation, a prevalence of commercial motives and a lack of patient involvement in key decisions are crucial factors that undermine the potential of the system to bring relevant innovations in a timely and more equitable way to those who need them. The growing complexity and sophistication of cancer research (reflected in increasing personalization and chronification) renders the challenge to do so even more acute.

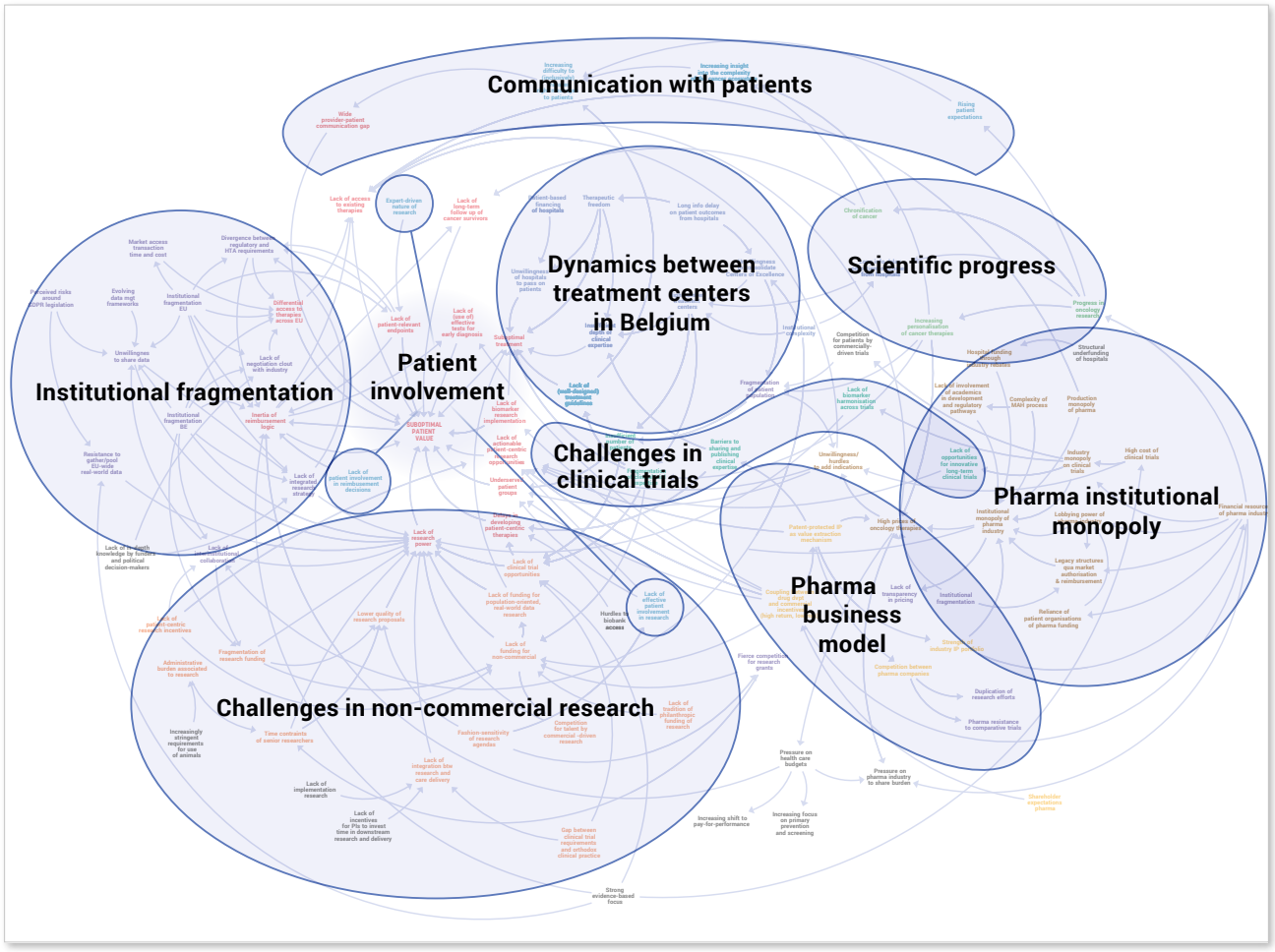


Figure 14: Overview of the clusters comprised in the diagnostic systems map of the Belgian oncology research system.

3.2 Aspirational model of a high-performance oncology research system

3.2.1 A SHARED VISION

The stakeholder trajectory ensured that the design of our aspirational model of a high-performance oncology research model was participatory. The resulting model was co-created by stakeholders and is therefore to a large extent supported by a wide range of stakeholders. It is an abstract representation of a system that is designed to generate patient value. It might be understood in terms of input and output. Inputs can be of any kind, including money, research efforts, the 'sweat and tears' of patients and caregivers; the purposeful human activity system that is labelled for convenience 'the oncology research system' transforms these inputs into value for cancer patients. It is an aspirational model in the sense that what is in the visual does not fully exist today. There is a gap between what we see happening now and what this model represents. The original scope of the research was focused on oncological research funded through public or philanthropic resources. However, the resulting activity model is generic and accommodates the contributions of both commercial and non-commercial actors as well as hybrid partnerships.

3.2.2 ARCHITECTURE OF THE ACTIVITY MODEL

The basic elements are conceptualised as activities, i.e. things that need to be done. Therefore, this abstract model in effect hides a very tangible and concrete reality because behind every box there are real people working to get something done. The combination of activities should realise the purpose that has been the guiding idea behind this research trajectory: to provide patients with rapid access to pertinent innovations from oncology research. In other words, the model is supposed to address the weaknesses of the current system when it comes to creating patient value. These weaknesses have been identified in the diagnostic part of the research process. Overall, the model represents a 'learning system' that constantly questions its own modus operandi as it is fed by evolving insight into patient value and its ability to fulfill patient needs.

Figure 15 displays the model. The model consists of 36 generic and interdependent activities. It represents a bird's eye view of a high-performance oncology research system. The activities can be grouped in five higher-order functional modules:

1. Defining and assessing patient value
2. Incentivising innovation
3. Agenda setting and funding
4. Conducting research
5. Learning by doing

The links between the activities present a logical dependency ('this can take place only if something else has taken place'). To give a simple example: first basic research needs to happen before translational research can take place (in the map 'Conduct Basic Research' feeds into 'Conduct Translational Research'). Similarly, before research goals can be prioritized, an inventory of goals needs to be consolidated in a research agenda (In the map 'Develop Research Agenda' feeds into 'Prioritize Research Goals').

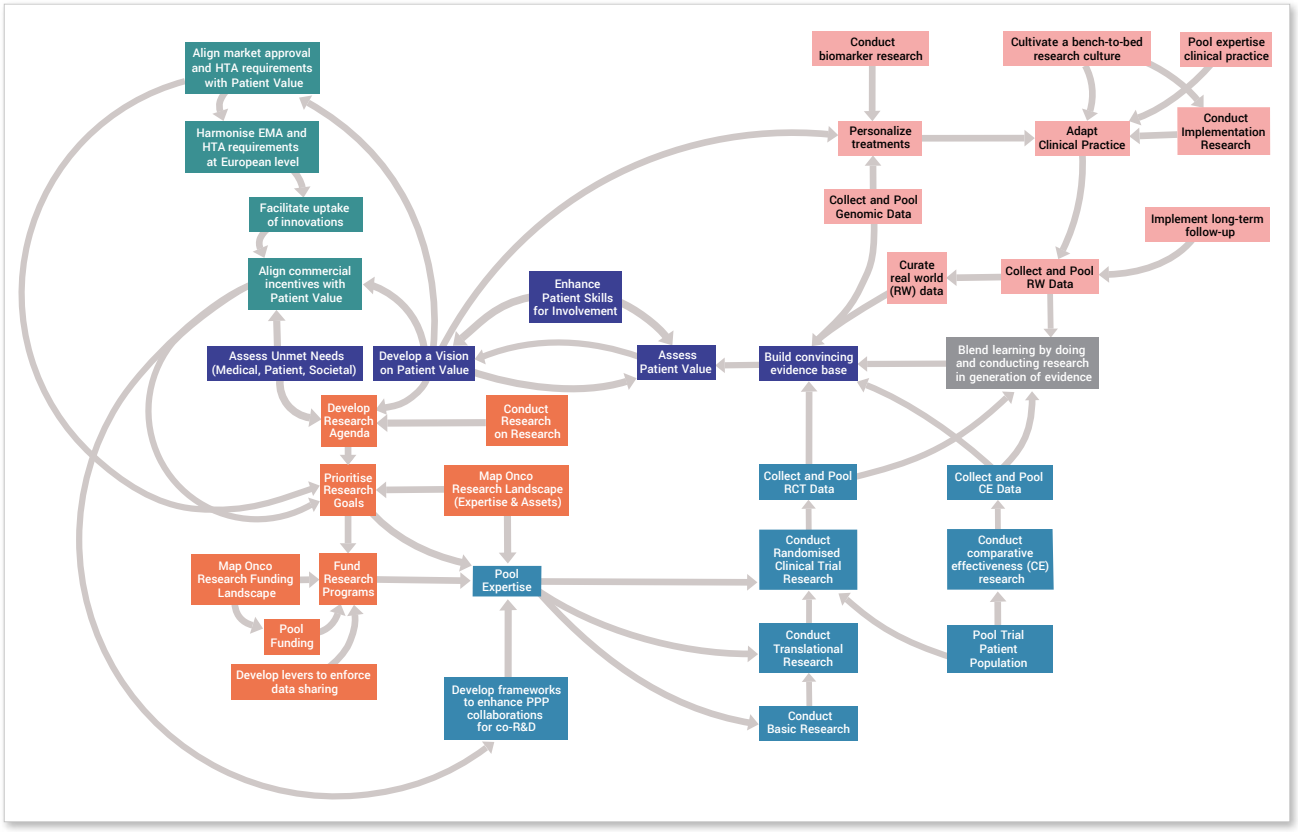


Figure 15: The aspirational model of a high-performance oncology research system.

3.2.3 DESCRIPTION OF MODULES

Defining and assessing patient value

The module 'defining and assessing patient value' is presented in Figure 16. The operationalization of an oncology research system that is driven by patient value requires envisioning what patient value is. This implies that stakeholders, including patients and their caregivers need to be concerned with developing a vision on patient value. And in addition, an assessment of patient value needs to be operationalized. Both activities, 'develop a vision on patient value' and 'assess patient value' are reciprocally linked. The one presupposes the other in a circular interaction. Meaning that the vision on patient value informs the way patients value is assessed, and vice versa. These two activities are informed by what patients themselves think and experience. The activity 'enhance patient skills for involvement' represents a necessary condition to include the voice of patients in the process of envisioning and assessing patient value. Two further activities are part of this cluster. Patient value can only be assessed if a convincing evidence base is put in place. The activity 'Build convincing evidence base' connects the core cluster 'defining and assessing patient value' with the clusters 'conducting research' and 'learning by doing'. From the description of these two clusters, it transpires that an evidence base is the result of the merging of data streams that emerge from distinct research tracks. Another important component that needs to provide guidance to the whole oncology research system is the appreciation of unmet needs. These unmet needs can be detected at the purely medical level, at the patient level and at the wider societal level[10]. Overall, the module 'defining and assessing patient value' anchors the aspirational model and lends it a fundamental orientation towards patient value and meeting unmet needs. It is the core of the system and provides a guiding purpose to it.

Incentivizing innovation

Grafted onto the core module is the module 'incentivizing innovation'. It represents the entrepreneurial engine that funnels resources into the oncology research system. See Figure 17. It is conceptualized as a combination of four activities. The two activities on the top are 'align market approval and HTA requirements with patient value' and 'harmonize EMA and HTA requirements at the EU level'. These are the metaphorical 'sticks' in the system as they harmonize requirements both at the geographical level and institutional level in line with patient value. These activities ensure that whatever enters the market is sure to contribute to patient value. The other two activities in the module aim to incentivize innovators to step into the system and to spend effort and resources in research and development. There are the 'carrots' as they are geared towards facilitating uptake of innovations and alignment of commercial incentives with patient value, for example via appropriate reimbursement mechanisms.

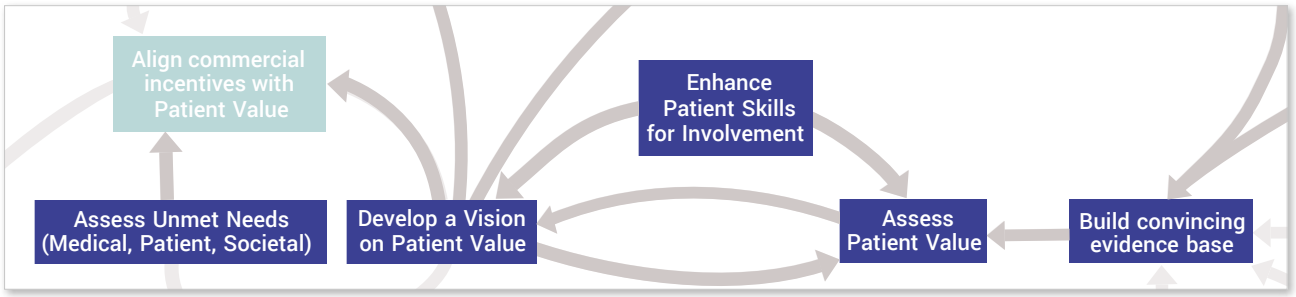


Figure 16: Detail of the module defining and assessing patient value.

10 The notion of 'unmet medical need' is not clearly defined, however; see R. A. Vreman, I. Heikkinen, A. Schuurman, C. Sapede, J.L. Garcia, N. Hedberg, D. Athanasiou, J. Grueger, H.G.M. Leufkens, W.G. Goettsch (2019) Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions, *Value in Health,* Volume 22, Issue 11, 2019, Pages 1275-1282, ISSN 1098-3015

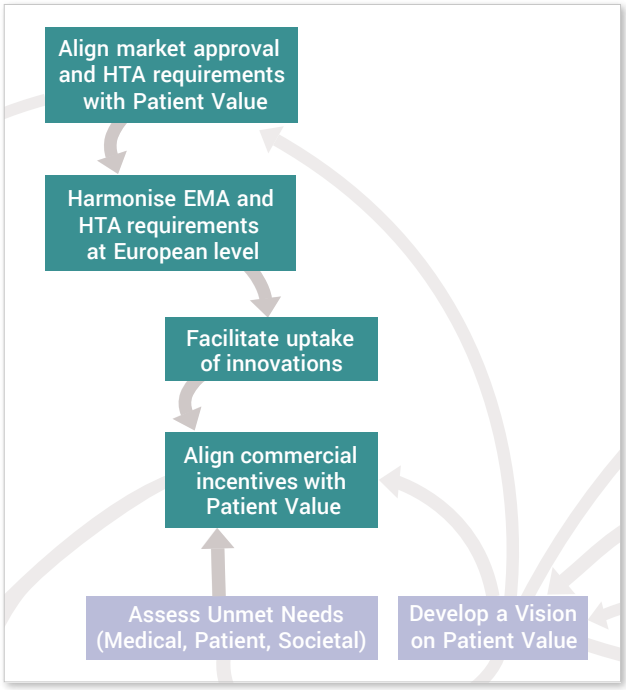


Figure 17: Detail of the module incentivizing innovation.

Agenda setting and funding

The two modules discussed above provide a broad orientation to efforts in the oncology research system in line with patient value and detected unmet needs. The present module translates this broad orientation into an actionable research agenda and makes sure that appropriate funding is allocated to it. An overview of this module is presented in Figure 18. An understanding of unmet needs and of patient value enables the development of a research agenda and allow for prioritization of research goals that leads to allocation of resources and funding. The two corresponding activities are 'develop research agenda' and 'prioritize research goals'. There are also several supporting activities in this module. A mapping of the research landscape in terms of available expertise and assets informs the prioritization of research goals. A similar mapping must happen with respect to funding. One needs to know what is available. The other two activities that are related to funding are 'pool funding' and 'develop levers to enforce data sharing'. One of the issues detected in the diagnostic part of the research is that funding streams are highly fragmented. Therefore, it would be good to include incentives and mechanisms to pool funding in the system. Lack of data sharing is another issue that has been identified as leading to suboptimal patient value. The desire to activate mechanisms to enforce data sharing can therefore be reflected in criteria that guide funding decisions. A final activity in this module is 'conduct research on research'. This is informed by the appreciation that the current oncological research system is evolving. It is dynamically adjusting itself to technological developments, evolving needs and changing policy and industry priorities. This change process needs to be informed by research at a meta level, i.e. research on research[11].

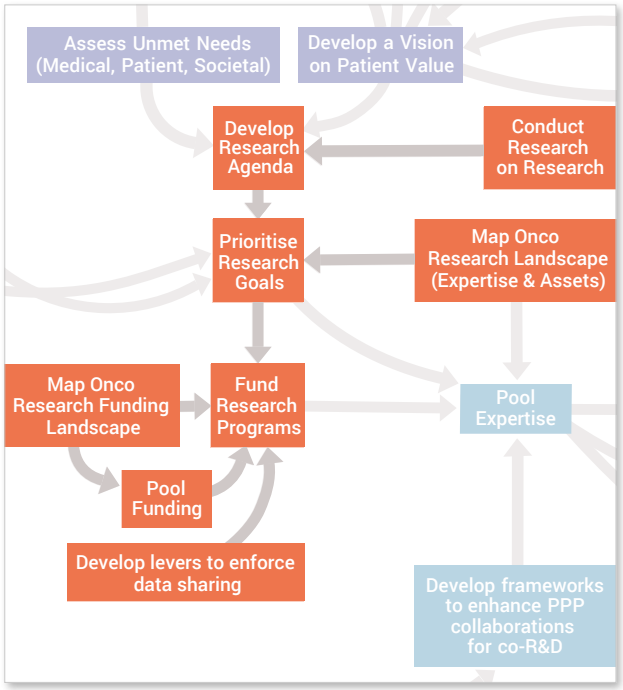


Figure 18: Detail of the module agenda setting and funding.

11 The recently established Research on Research Institute, hosted by the Wellcome Trust and not limited to oncological research, describes the scope of its activities as "develop theoretical frameworks, standardize methods, strengthen networks, and test the transferability of approaches from one context to others" (http://researchonresearch.org/about).

Conducting research

The module 'conducting research' represents a conventional way of looking at the oncology research chain from basic or fundamental research to translational research to clinical research, cfr. Figure 19. This core of the module is complemented with a comparative effectiveness research track (aimed evaluating and comparing the implications and outcomes of two or more health care strategies to address a particular medical condition, typically the innovation versus usual care). The data that result from these research tracks have to be collected and pooled. These information management activities then feed into 'build a convincing evidence base'. An additional important activity needs to ensure that trial patient populations are pooled to support both clinical and comparative effectiveness research. All research activities have to be fed by appropriate expertise. Therefore 'pool expertise' is an activity that feeds into the core oncological research chain. In the diagnostic part of our analysis, fragmentation of expertise, particularly also at the Belgian level, was put forward as one of the drivers leading to lack of research power resulting in downstream suboptimal patient value. Funding mechanisms can provide an incentive for the pooling of expertise. The final activity included in this module is the development of frameworks to enhance Public-Private Partnerships (PPP) for collaborative R&D. This activity links the commercial incentives (from the incentivizing innovation module) to the pooling of expertise.

Learning by doing

The final module is 'learning by doing' and is presented in Figure 20. This is the realm of clinical practice and real-world (observational) data[12]. Real-world data are tapped from an evolving clinical practice and from long-term patient follow-up. Given the heterogeneous nature of these data it is important to curate them in appropriate way to allow them to contribute to a convincing evidence base. Ideally, the continued development of clinical practice is driven by a bench-to-bed research culture (to make sure that clinicians are receptive to research-driven innovations), targeted implementation research (to facilitate the actual uptake of innovations in the practice), and the pooling of clinical practice expertise. The personalization of treatments is another activity that feeds into an evolving clinical practice. Personalization is driven by a vision on

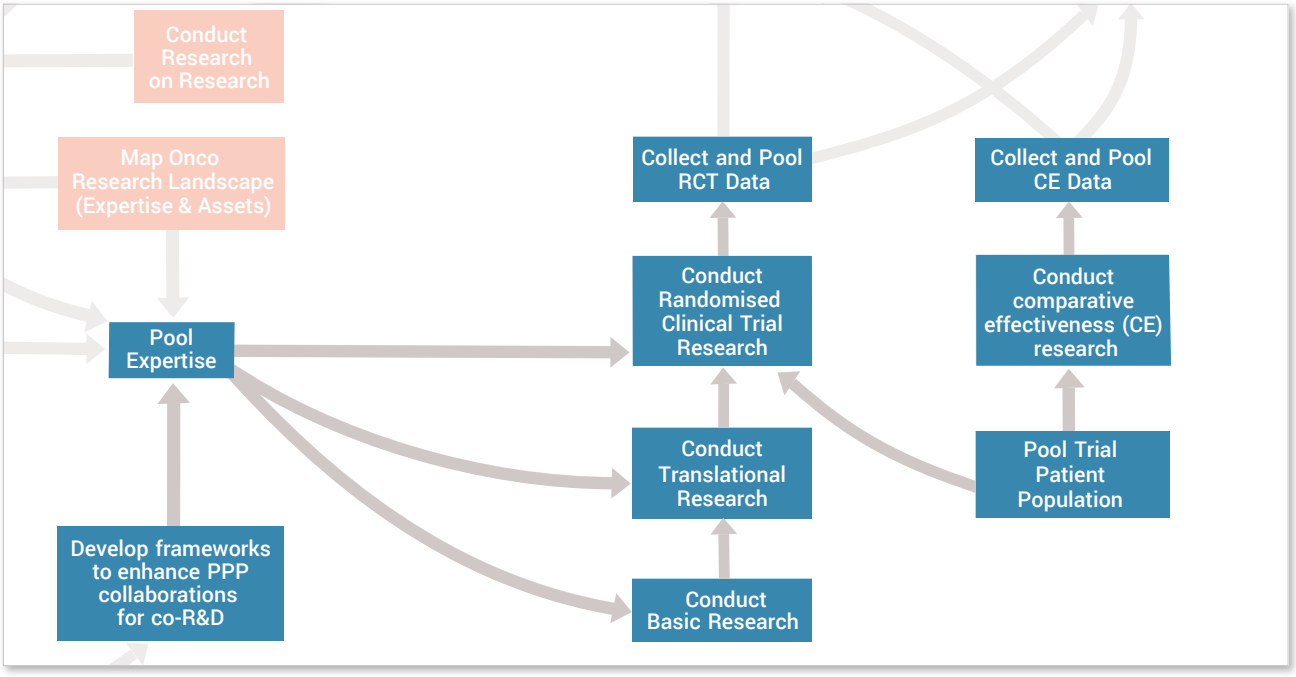


Figure 19: Detail of the module conducting research.

12 E. Skovlund, H.G.M. Leufkens and J.F. Smyth (2018) The use of real-world data in cancer drug development, *European Journal of Cancer*, Vol. 101, p. 69-76.

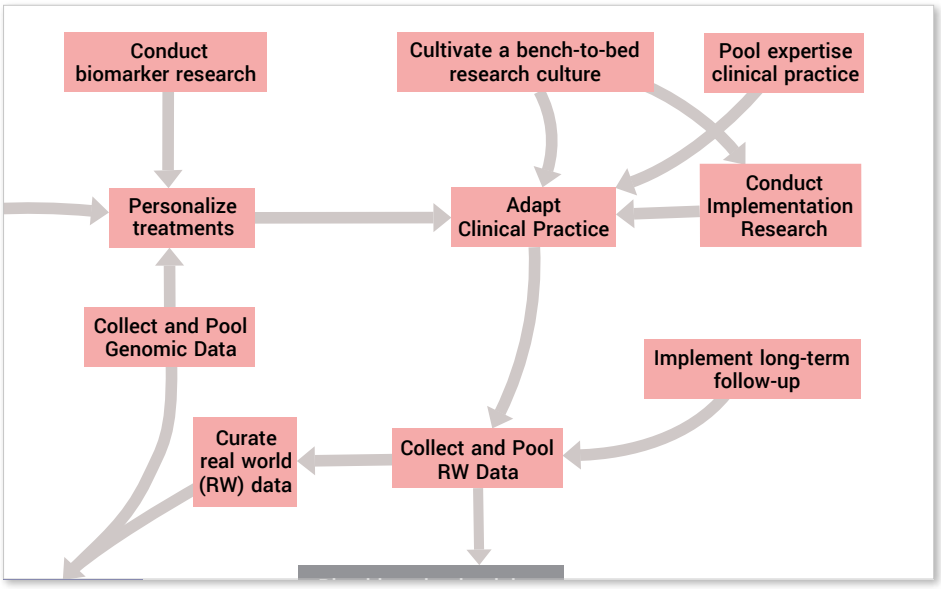


Figure 20: Detail of the module learning by doing.

patient value and enabled by the collection and pooling of genomic data and by biomarker research. The activity 'personalize treatments' feeds into 'adapt clinical practice' and forms together with real-world data and the core module around patient value the learning cycle in the module 'learning by doing'.

Blending learning by doing and conducting research in generation of evidence

There is another activity in the model that does not belong to any of the clusters discussed above but is standing on itself, namely 'blending learning by doing and conducting research in generation of evidence' as presented in Figure 21. Two research clusters are embedded in the overall aspirational model. The 'conducting research' cluster reflects a strongly evidence-driven logic, while in the 'learning by doing' cluster research is carried out in an action research mode. Stakeholders believed these two fields need to be blended. Hence the inclusion of a separate activity. All the different data streams from the core research chain, from comparative effectiveness research and from the real-world data, blend into building a convincing evidence base, which feeds into the assessment of patient value which bring us back to the core module 'defining and assessing patient value'.

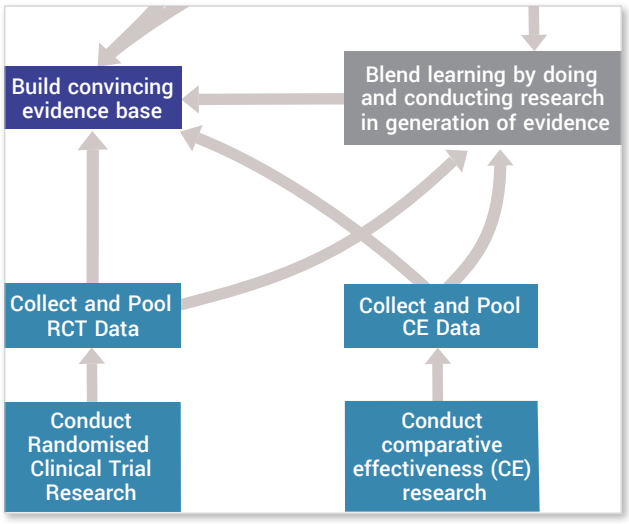


Figure 21: Detail of the activity 'blend learning by doing and conducting research in generation of evidence'.

3.2.4 SUMMARY

The developed aspirational model of a high-performance oncology research system provides a vision that addresses the weaknesses of the current oncology research system identified in the diagnostic systems map. It was co-created with a broad range of stakeholders and reflects a shared vision of how the Belgian oncology research system might take shape as a human activity system designed to optimize patient value. In that sense, the model offers an aspirational, purposeful outlook whilst building awareness of the whole system and the orchestration of all aspects related to research, including agenda setting, funding, and incentivizing. The connection between conducting research and learning by doing in the model provides a foundation for dialogue and action in the light of the growing complexity and sophistication of cancer research as reflected in increasing personalization of treatments. The model is generic and accommodates the contributions of both commercial and non-commercial actors as well as hybrid partnerships. Overall, the aspirational model holds potential to serve as a catalyst in the process of moving towards a high-performance oncology research system.

3.3 Recommendations

3.3.1 OVERVIEW

The aim of the third stakeholder workshop was to gather recommendations for improvements to the current oncology research system in the light of the aspirational model. Table 1 provides an overview of the recommendations resulting from the subgroup discussions in the workshop. All recommendations were presented in a plenary session which resulted in additional fine-tuning. They therefore embody perspectives and aspirations from different stakeholders.

TABLE 1: Overview of recommendations from stakeholders for improvements to the current oncology research system.

1. Integrate patients in research agenda setting and funding decisions.
2. Create a platform for integration of different data streams.
3. Install fair pricing mechanism.
4. Operationalize the assessment of unmet needs.
5. Leverage data sharing.
6. Enhance collaboration of/with HTA/ regulatory bodies.
7. Develop trial programs that assess added patient benefit with speed and flexibility.
8. Facilitate access to innovative therapies in clinical studies for rare gene abnormalities/ rare tumors independent of location of center and patient.
9. Differentiate survivorship research by age cohort.
10. Secure buy-in for the vision reflected by the aspirational oncological research model.
11. Build capacity and capability of researchers to do holistic 'patient-centered' research and users to use research.
12. Mobilize/recognize/support GPs as key partners in prevention, early diagnosis, research and survivorship.

3.3.2 DISCUSSION OF RECOMMENDATIONS

Recommendation 1

Integrate patients in research agenda setting and funding decisions

ACTION: This recommendation comprises two actions. The first one is to establish a (national) platform geared towards the assessment of unmet needs. These unmet needs can be articulated at different levels ranging from purely medical to the societal level. The platform also needs to ensure that defining unmet needs is done in collaboration with patients or developed bottom-up by patient groups. The second action involves the translation of unmet needs into a research agenda while maintaining dialogue with patients. In a broader sense, design and evaluation of new research proposals should be done in collaboration with patients, not only regarding the subject, but also the process of the research. It was suggested that the involvement of patients is particularly important in translational and clinical research. In the Netherlands, some professional societies and patient associations prioritize together the research questions in their field.

STARTING POINT: Existing patient advisory boards (for example embedded in Kom op tegen Kanker or operational at University Hospital Ghent, where they give input to the evaluation of research proposals) could combine their insights, share their experiences, and join forces as a step-up to establish a patient advisory board at the national level.

CHAMPION AND ACTORS: The ambassador or champion should be one or more patient organizations at the national level. In addition, universities and research centers need to be involved both to play a role in the assessment of unmet needs, but also to direct their research agenda to address these unmet needs. The federal and regional governments ideally are involved in the assessment of societal unmet needs and steering of the research funding towards the identified unmet needs.

CRITICAL FACTORS: There is a need for educated and trained patients, especially for the evaluation of research proposals. It also needs to be ensured that the vision of patient value is reflected in the logic of research funding. In other words, ensure that the funding of research is conditional and that the outcomes are safeguarded against capture by purely economic interests. And lastly, the connection with the European context and international context needs to be considered from the early stages.

Recommendation 2

Create a platform for integration of different data streams

ACTION: The proposed action aims at the creation of a platform to integrate different research-driven data streams. These data should be made available in a centralized way for research purposes via cancer registers. It was suggested that assuring availability of data and the integration of real-world data should be prioritized. More specifically, a code of conduct should be established that states what type of data could be accessed for what purpose and by which type of organization. In addition, integration of new technologies comprising for example artificial intelligence could be integrated in such platform. This would align well with the context of more personalized approaches in cancer treatment. The integration of data streams feeds into the assessment of patient value. And it would also allow to identify unmet patient needs.

STARTING POINT: The Belgian Cancer Registry already makes data available for researchers for doing research on specific research questions while considering GDPR rules. As a first step, a pilot study or proof-of-concept was suggested to see how the integrated platform could work whilst including hospital and health care data.

CHAMPION AND ACTORS: The Belgian Cancer Registry could take a lead role because it has an established and a well-organized data collection system at population-based level. Sciensano, RIZIV-INAMI and regional and federal governments were added to the list of stakeholders.

CRITICAL FACTORS: The most critical issue with respect to data are the hurdles related to GDPR, especially for data sharing and using data for research

purposes. Another element brought to the table by the workshop participants was that of cross-linking data at a European level. EU is advancing towards digital health including the use of standards for coding like SNOMED. Inspiration may be sought from the Rare Disease clinical research network and their efforts to centralize data at the European level.

Recommendation 3

Install a fair pricing mechanism

ACTION: The action proposed during the workshop is to take the definition of fair price and fair pricing from the European Cancer Leagues as the underpinning principle of the reimbursement mechanism. Herein, a fair price is defined as justifiable, predictable, and cost-effective within the aims and priorities of the healthcare systems and the available budget. At the same time, a fair pricing policy that considers the ethical and financial dimensions of patient access to care, affordability and sustainability of healthcare systems should be encouraged and rewarded.[13] During the workshop, the definition of a fair price was articulated in a slightly different way. A fair price needs to be linked with clinical benefit or patient value. In addition, there must also be a 'reasonable relationship' with the underlying costs of the developed drug, i.e. costs for R&D and cost of goods. And finally, the fair price should have a reasonable budget impact. Because otherwise, the price will not be sustainable. To realize this fair price, it was mentioned that there should be more transparency in the system, for example transparency of underlying costs. The recommendation fits with the activity 'align commercial incentives with patient value' in the aspirational model because commercial value is strongly connected with the price of a drug.

STARTING POINT: It was mentioned that already many discussions are ongoing about fair pricing, because many stakeholders perceive it as a challenge to align commercial incentives with patient value. When moving forward, connection should be sought with the existing endeavors.

CHAMPION AND ACTORS: The European Cancer Leagues who proposes the definition of fair pricing could take the champion role. Driving the action forward would require a multi-stakeholder coalition including research organizations, industry, public health authorities and the European Commission.

CRITICAL FACTORS: One critical factor may be the involvement of the pharmaceutical industry.

Recommendation 4

Operationalize the assessment of unmet needs

ACTION: The suggestion was to set-up an observatory at European level for unmet needs. This observatory could take care of a combination of consultation types, such as surveys, focus groups or direct dialogue with all stakeholders involved. In such way, the continuous and ongoing consultations in the process of optimizing patient value becomes a permanent effort rather than a one-off exercise. It is considered important to consolidate relationships.

STARTING POINT: The methodology that is used by the European Commission to consult with citizens could be useful. It would make sense to reach out to actors who can drive this type of consultations (researchers and patient organizations). To identify needs at societal level, payers should be consulted.

CHAMPION AND ACTORS: At the European level, professional organizations such as the European Cancer Organization and perhaps the European Society for Medical Oncology are considered important actors. Of course, European patient organizations should be included as well. Unmet needs are supposed to drive research and innovation and therefore, the national point of contact that feeds in from the member state of Belgium to the EU Cancer Mission, should also be considered as an important actor. National foundations and charities, the European public health organizations and EMA were mentioned as well.

CRITICAL FACTORS: Consultation of perspectives on unmet needs must be organized in an inclusive way.

13 https://www.europeancancerleagues.org/wp-content/uploads/ECL-What-is-a-Fair-Price-Paper_final.pdf

Recommendation 5

Leverage data sharing

ACTION: Install mechanisms to leverage use and sharing of data and biological materials. The latter is related to translational clinical research. Data and biological materials should be made available for secondary purposes and to the broader research and multi-stakeholder community for follow-up research. Also funding agencies should be enabled to have access to that data. And governments are an important stakeholder to set the agenda right in terms of research and funding and clinical research, in the sense that evaluation of institutes and research should also be re-evaluated in the sense that the KPI's that are put forward should also take into account the societal impact. Societal valorization should also be measurable, as opposed to only economical valorization. The subgroup also suggested to make individual patient data more accessible to the community through the EMA.

STARTING POINT: The suggestion was to start with a visualization of all hurdles to the above-mentioned sharing of data and biological materials. In addition, currently existing best practices should be made more visible. This could be a big inspiration, to come up with true guidelines.

CHAMPION AND ACTORS: The European Commission and EMA are important actors. In the context of valorization, tech transfer offices, IP-regulators and all actors involved in funding will have an important role to play when engaging into a dialogue about sharing of data and biological materials. At the national level, the cancer registry could take on a champion role.

CRITICAL FACTORS: The overarching context of privacy of personal data and research data as asset for valorization could be hampering in a general sense.

Recommendation 6

Enhance collaboration of/with HTA/regulatory bodies

ACTION: The suggestion was to ensure that the worlds of the regulators with the health technology assessment agencies, the payers, the clinicians, and the patients are brought together. The parties could define the expected evidence together. This should be achieved with the right evidentiary standards, the right evidentiary requirements and clarification around when do we need to ask the right questions and at what point. This action could include making the therapeutic benefit part of the regulators' criteria. The subgroup explained that this would certainly require legislative changes because it really touches upon the core of the current mandate of the regulators and the EMA. Because this would be a significant stretch, the subgroup elaborated on a starting point which could bring HTA requirements closer to the regulatory process.

STARTING POINT: The HTA requirements could be brought closer to the regulatory process through the channel of scientific advice, which is something that is currently used in practice. This would imply that the regulators take the HTA requirements much more into account in the scientific advice and in the assessment and approval process. This connects in the aspirational model with the activity 'harmonize EMA and HTA requirements at European level'. One should be aware that the HTA advice remains non-binding in the current scientific advice process as a pre-submission activity.

CHAMPION AND ACTORS: The subgroup identified a series of actors, starting with HTA bodies and regulators. There needs to be more coordination and cohesion amongst HTA bodies. In addition, they need to be closer and working more efficiently together with the regulators, both at the national level, and on the European level with EMA. Another important actor closely tied to HTA bodies are the payers. It was mentioned that there currently are discussions between the payers, HTA bodies and the EMA. Those need to be streamlined, intensified, to ensure better results and outcomes for patients. The pharmaceutical industry and non-commercial funders of research are key actors in this constellation

as well. An important point raised was that this recommendation and connected activity 'harmonize EMA and HTA requirements at European level' can only be achieved with the right dose of political will. The champions for changes must come from the ministries of health and because of the financial implications of their decisions, they should be supported by the ministries of finance. In addition, patient organizations and health care professionals and their societies also can take up a champion role.

CRITICAL FACTORS: Obviously, there would have to be political pressure, possible legislation change, introduction of sanctions in the case of non-compliance. There should also be incentives for the pharma-industry to generate additional evidence. In this respect, additional actions such as a conditional reimbursement, and use this conditional reimbursement as a point of leverage to get the necessary additional evidence we need, could be considered. Another critical factor is the current fragmentation between the regulators and HTA but also amongst national HTA bodies in Europe.

Recommendation 7

Develop trial programs that assess added patient benefit with speed and flexibility

ACTION: This recommendation comprises four actions. The first action is to develop and introduce innovative designs for oncology clinical trials. The experience with multi-arm randomized trials for covid-19 could serve as a learning opportunity. It must be ensured that these designs are robust and statistically valid. The second action is to bring regulators, HTA and patients closer together by means of including aspects from comparative effectiveness into pivotal trials and include patient-relevant endpoints. A third action is to harmonize clinical trial designs, especially when it concerns similar therapeutic classes, for example in the case where each drug developing its own companion diagnostic without any harmonization, which makes it impossible for oncologists to select or to have available all companion diagnostics. A fourth action is to develop training on research, including the more complex study designs, so that everyone is aware of the possibilities and the limitations and strength.

STARTING POINT: A starting point could be to leverage the learnings from the covid-19 clinical trials to the oncology research arena.

CHAMPION AND ACTORS: The essence of recommendation 7 is to bring valuable innovation, more rapidly to patients. The relevant actors include EMA, governments, payers, regulatory bodies at the national level, academics, health care professionals and their organizations, the pharmaceutical industry, funders of clinical research and patients their organizations. Champions should be skilled in the art of clinical research and operate at the European level. Mario Negri Institute, the European Organization for Research and Treatment of Cancer and the Anticancer Fund are well positioned to take a leading role. Other suggestions were the ministers of health, but also patient organizations to help this being realized. Additionally, scientific journals and health care professional societies are expected to play a critical role as well.

CRITICAL FACTORS: Novelties in designs need a lot of discussion with the regulators and a critical review before they will be accepted. Also, because some of these designs have sub-optimal methodologies, a clinical review remains essential.

Recommendation 8

Facilitate access to innovative therapies in clinical studies for rare gene abnormalities/ rare tumors independent of location of center and patient

ACTION: The fragmentation of the patient population underlies the activity 'pool trial patient population' of the aspirational model. It should be ensured that clinical research centers are able to open clinical trials in 3 to 4 weeks in order to treat patients with specific, very are abnormalities in the context of personalized treatment. It also provides a part of the answer to the blurring of clinical research phases.

STARTING POINT: This action could be initiated with a small network of clinical research centers.

CHAMPION AND ACTORS: Networks of clinical research centers are considered critical.

CRITICAL POINTS: This effort will only be successful if sufficient scale is obtained at the European level. This implies a change in regulatory processes at both national and EU level.

Recommendation 9

Differentiate survivorship research by age cohort

ACTION: Survivorship encompasses clinical, social, and psychological research and it depends on the age of the patient. It is vital to cover different needs and aspects for different age categories in survivorship research. This will enable to approach survivorship more precisely. This action connects to the activities 'personalize approach' and 'adapt clinical practice' of the aspirational model.

STARTING POINT: Not mentioned.

CHAMPION AND ACTORS: The actor constellation includes psychologists, primary care providers, social workers, health insurances and political decision makers.

CRITICAL FACTORS: The action should capitalize on existing pilot initiatives and international experience, such as in The Netherlands, to be successful.

Recommendation 10

Secure buy-in for the vision reflected by the aspirational oncological research model

ACTION: The subgroup voiced that the current stakeholder trajectory resulted in an aspirational model that inspires. The obvious next step is to extend the stakeholder consultation while focusing on the outcomes of the current stakeholder trajectory. The aim should be to secure buy-in of a broad stakeholder community.

STARTING POINT: The aspirational model is presented at an abstract level. Translating this model into accessible language tailored to the relevant stakeholder will be important. This could be achieved by giving real examples. It was also suggested to write a scholarly paper/commentary paper for an impactful journal. In addition, alternative dissemination formats (e.g. TED-like talk for clinical research centers) should be considered.

CHAMPION AND ACTORS: The KBF were suggested to take on the champion or ambassador role. The actors are everyone who is involved in the oncology research system, including patients and their organizations, health care providers, researchers, funders, policy makers, the pharmaceutical industry and pharma.be, regulators and first line care providers, i.e. general practitioners.

CRITICAL POINTS: The readability of the model could be a challenge for some persons. This could be remediated by providing examples of activities of which the model is composed. Finally, the buy-in from pharmaceutical industry could be challenging to achieve.

Recommendation 11

Build capacity and capability of researchers to do holistic 'patient-centered' research and users to use research

ACTION: There is a need for investment in building capacity and capability in doing systemic research that is patient centric. It is important to recognize that another type of research mindset is needed and that it needs to be cultivated. Researchers should be able to see the whole oncology research systems and they should develop the skills to have a meaningful dialogue with actors working on other aspects.

STARTING POINT: Funding of researchers such as PhD students or post-doctoral fellows. Training could also be a means to install a more holistic research culture. The Mario Negri Institute could serve as an inspiration for this recommendation.

CHAMPION AND ACTORS: Universities probably are the main actor and thus champion for this recommendation.

CRITICAL FACTORS: Moving from siloed research to systemic research will require the design of appropriate incentives and a framework that bridges (academic) research centers at an operational

level. Incentives for academic researchers such as publications, patents filed, and research contracts funded by industry may not be the most appropriate to improve patient value.

Recommendation 12

Mobilize/recognize/support GP's as key partners in prevention, early diagnosis, research, and survivorship

ACTION: The central idea behind this recommendation is that first line health services, providers, GP's are considered as key partners in the 'development of a bench-to-bedside research culture', in 'the implementation of long-term follow-up' and in 'conducting implementation research'. They could play a role in providing the whole system with information concerning patients and help in gathering real-world data. They could also play a role in referring end-of-treatment patients to the appropriate experimental treatments if they are supported by an evidence-based information service.

STARTING POINT: Not mentioned.

CHAMPION AND ACTORS: This recommendation needs funders who want to invest in this type of research. Suggestions coming from the subgroup were Kom op tegen Kanker and Cancer Research UK. Champions for this recommendation include KBF, more specifically Fund Dr. Daniel De Coninck. Other important actors include Domus Medica/SSMG and the Royal College of General Practitioners.

CRITICAL FACTORS: Clinical pathways need to be adapted to facilitate access of patients to adequate trials and to centers of excellence. This recommendation also requires clearly identifiable centers of expertise.

3.3.3 SUMMARY

The recommendations aim to improve the current oncology research system and move towards the shared vision of the aspirational model. As such they provide an actionable bridge between the weaknesses addressed in the diagnostic systems map and the aspirational model designed to optimize patient value. Figure 22 maps the set of recommendations onto the aspirational model of a high-performance oncology research system. Overall, the stakeholder workshop resulted in a set of recommendations spread out over the entire model; five out of twelve recommendations are associated with the core module of the activity model, i.e. defining and assessing patient value. This confirms the importance of developing a defensible and patient-informed approach to the challenge of defining and assessing patient value. It is important to note that the set of recommendations is not comprehensive nor final. They illustrate how to prioritize actions when using the aspirational model as the starting point. And they also provide a basis to strategize the way forward in concerto with the stakeholders in the Belgian oncology research system.

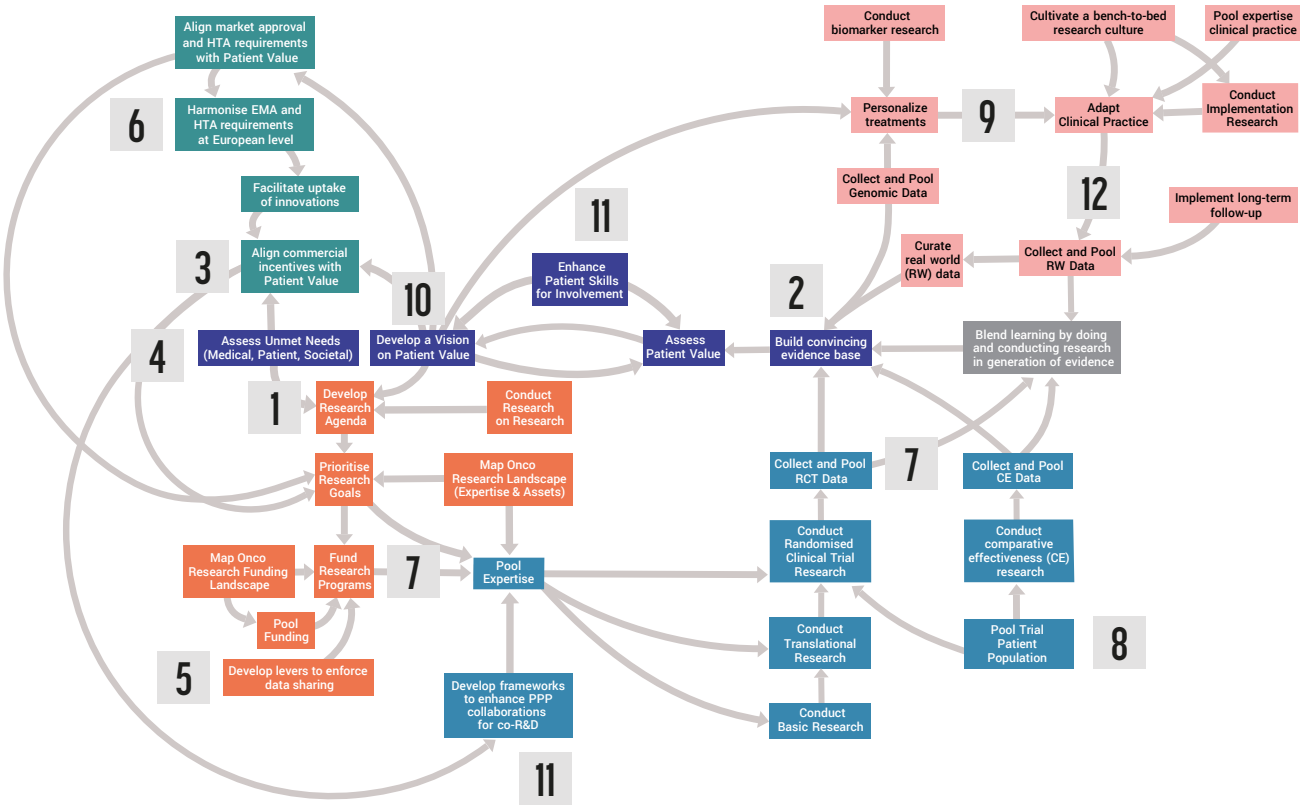


Figure 22: The set of recommendations mapped onto the aspirational model of a high-performance oncology research system.

4 CONCLUSIONS

Cancer is a significant challenge for society, healthcare systems and the growing number of affected patients and their families. The question put forward by KBF as starting point for the strategic reflection was as follows: 'How can we ensure that cancer patients have rapid and affordable access to the results of evidence-based, publicly and philanthropically funded studies, to improve their life expectancy and quality of life?' A broad group of stakeholders was assembled to reflect on this question and to propose recommendations for improvement. The group represented key actors in the Belgian oncology research landscape, complemented with several international experts. They were supported through a disciplined process of exploration of the factors that lead to suboptimal patient value in the Belgian oncology research system. Building on these insights the stakeholder group proposed a conceptual model of a high-performance oncology research model designed to remedy the weaknesses of the existing research system.

The exploration phase resulted in a clear, communicable problem definition, and in-depth insights on why the current oncology research system leads to suboptimal patient value based on a systems mapping approach. The diagnostic systems map also reflects that it is conceptually not possible to consider the oncology research system funded by public and philanthropic resources as separate from an industry-funded research system. They interact with one another in myriads of ways. Based on this map one can argue why the current oncology research system is not well equipped to generate patient value. This insight delivered a connecting sense of urgency.

The design phase delivered a shared vison on the design of an aspirational model of a high-performance oncology research system. The model reflects a vision that deliberately counters the weaknesses of the current oncology research system identified in the diagnostic systems map. The model is generic and demonstrates a functional logic. In other words, it reveals what the essential functions or activities are that need to be fulfilled in a research system that is rigorously oriented towards generating patient value. The model accommodates the contributions of both commercial and non-commercial actors as well as hybrid partnerships. The aspirational model holds potential to serve as a catalyst in the process of federating and aligning key actors in the oncology research system behind the ambition to create patient value.

The final deliverable of this strategic reflection is a set of recommendations that enfold perspectives and aspirations from different stakeholders. The recommendations lay out an action-oriented agenda to move towards the shared vision reflected by the aspirational model. As such they provide an actionable bridge between the weaknesses pointed out by the diagnostic systems map and the aspirational model designed to optimize patient value. The recommendations span the full scope of the latter, addressing challenges related to assessment of patient value, policy, agenda setting, funding, and setting up research studies. It is important to note that the set of recommendations is not comprehensive nor final. The set of recommendations therefore provide a solid basis to strategize the way forward in concert with key stakeholders in the Belgian oncology research system.

It is hoped and expected that this process puts in place a basis for a strategic process of transitioning towards a future in which patients will benefit more from the enormous resources that are mobilized to combat cancer. Securing buy-in from a broader coalition of stakeholders in Belgium and beyond will be key to maintaining the momentum and expanding the scope of the transition. The KBF has the intention to continue to play an energetic role in this process.

5 PARTICIPANT LISTS

5.1 Interview campaign

Ahmad Awada (Jules Bordet Institute), Catherine Vanderstraeten (Health, innovation and research institute UZ Gent), Delphine Heenen (KickCancer), Denis Lacombe (European Organisation for Research and Treatment of Cancer), Didier vander Steichel (Fondation contre le Cancer), Elisabeth Van Eycken (Belgian Cancer Registry), Francesco Pignatti (European Medicines Agency), Frank Hulstaert (Belgian Health Care Knowledge Centre), Jo De Cock and Marc Van De Casteele (RIZIV/INAMI), Kristel De Gauquier (Pharma.be), Lydie Meheus (Anticancer Fund), Marc Van den Bulcke (Sciensano), Marianne Ghyoot (Biowin), Maurizio D'Incalci (Mario Negri Institute), Nora Pashayan (University College London), Antonella Cardone (European Cancer Patient Coalition), Rudy Dekeyser (Life Science Partners), Sabine Tejpar (University of Leuven), Sylvie Rottey (UZ Gent), Ward Rommel (Kom op tegen Kanker)

5.2 Online stakeholder consultation (diagnostic systems map)

Ahmad Awada (Jules Bordet Institute), Catherine Vanderstraeten (Health, innovation and research institute UZ Gent), Arnaud Goolaerts (Fond de la Recherche Scientifique), Damya Laoui (Vrije Universiteit Brussel – Flemish Institute for Biotechnology), Delphine Heenen (KickCancer), Denis Lacombe (European Organisation for Research and Treatment of Cancer), Patricia Servais (Fondation contre le Cancer), Frank Hulstaert (Belgian Health Care Knowledge Centre), Kristel De Gauquier (Pharma.be), Lydie Meheus (Anticancer Fund), Marc Van den Bulcke (Sciensano), Marianne Ghyoot (Biowin), Nora Pashayan (University College London), Rudy Dekeyser (Life Science Partners), Ward Rommel (Kom op tegen Kanker)

5.3 Small group brainstorm sessions

Session 1: Delphine Heenen (KickCancer), Lydie Meheus (Anticancer Fund), Rudy Dekeyser (Life Science Partners); *Session 2:* Catherine Vanderstraeten (Health, innovation and research institute UZ Gent), Denis Lacombe (European Organisation for Research and Treatment of Cancer), Kristel De Gauquier (Pharma.be), Ward Rommel (Kom op tegen Kanker); *Session 3:* Ahmad Awada (Jules Bordet Institute), Damya Laoui (Vrije Universiteit Brussel – Flemish Institute for Biotechnology), Patricia Servais (Fondation contre le Cancer), Marc Van den Bulcke (Sciensano), Marianne Ghyoot (Biowin)

5.4 Second stakeholder workshop (aspirational activity model)

Ahmad Awada (Jules Bordet Institute), Damya Laoui (Vrije Universiteit Brussel – Flemish Institute for Biotechnology), Delphine Heenen (KickCancer), Denis Lacombe (European Organisation for Research and Treatment of Cancer), Frank Hulstaert (Belgian Health Care Knowledge Centre), Iain Foulkes (Cancer Research UK), Jean-Benoît Burrion (Jules Bordet Institute), Kristel De Gauquier (Pharma.be), Lydie Meheus (Anticancer Fund), Marc Van den Bulcke (Sciensano), Marianne Ghyoot (Biowin), Mef Christina Nilbert (Danish Cancer Society), Nancy Van Damme (Belgian Cancer Registry), Olga Kholmanskikh (Federal Agency for Medicines and Health Products), Rita Banzi (Mario Negri Institute), Nora Pashayan (University College London), Antonella Cardone (European Cancer Patient Coalition), Rudy Dekeyser (Life Science Partners), Sofie Bekaert (Flemish Institute for Biotechnology), Ward Rommel (Kom op tegen Kanker), Yannis Natsis (European Public Health Alliance)

5.5 Third stakeholder workshop (recommendations)

Ahmad Awada (Jules Bordet Institute), Damya Laoui (Vrije Universiteit Brussel – Flemish Institute for Biotechnology), Catherine Vanderstraeten (Health, innovation and research institute UZ Gent), Frank Hulstaert (Belgian Health Care Knowledge Centre), Jean-Benoît Burrion (Jules Bordet Institute), Lydie Meheus (Anticancer Fund), Nancy Van Damme (Belgian Cancer Registry), Olga Kholmanskikh (Federal Agency for Medicines and Health Products), Rita Banzi (Mario Negri Institute), Nora Pashayan (University College London), Antonella Cardone (European Cancer Patient Coalition), Sofie Bekaert (Flemish Institute for Biotechnology), Ward Rommel (Kom op tegen Kanker) Yannis Natsis (European Public Health Alliance)

6 LIST OF ABBREVIATIONS

EU	European Union
EMA	European Medicines Agency
GP	General Practitioner
HTA	Health Technology Assessment
INAMI	Institut national d'assurance maladie-invalidité
KBF	King Baudouin Foundation
R&D	Research & Development
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering
SNOMED	Systematized Nomenclature of Medicine Clinical Terms