Master's thesis: MSc Innovation Sciences

From Invention to Innovation: An Institutional Perspective on AI Developments in the Haemato-Oncological Field

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ABSTRACT

Unravelling cell characteristics is key for the accurate diagnosis and treatment of haemato-oncological diseases. Major advancements in the field have led to high-throughput single-cell technologies, providing large and multidimensional datasets. Detecting the relevant information in these datasets remains a challenge, however. Artificial intelligence (AI) can support the human capability and can thereby prove to be the next step in improving patient survival rates. However, although the academic interest in AI developments is substantial, the real-world deployment remains behind. This was referred to as *the invention-innovation gap,* invention being an idea, and innovation being the commercialization of that idea.

Starting from the idea that innovation does not happen in isolation but is part of a system, both the institutional and technological environment are crucial for an invention to become an innovation. In that line of thought, institutional entrepreneurs are actors that actively transform the institutional environment in favour of an emerging technology. In this research, it was examined ***whether the haemato-oncological field offers an enabling environment for institutional entrepreneurship to occur in the context of AI technologies***.

The institutional entrepreneurship approach was specified for the haemato-oncological field with domains of the non-adoption, abandonment, scale-up, spread and sustainability (NASSS) approach, a framework designed to study failure of innovation in the medical field. An explorative, qualitative research design was followed, using a single case study. Data was gathered through 18 semi-structured interviews and triangulated by 10 expert events. An abductive approach was followed, starting from prior theoretical knowledge, subsequently translating empirical findings into theoretical contributions.

This paper presents an extensive description and in-depth analysis of the key findings. This resulted in four technological prerequisites that should be fulfilled to provide an environment in which institutional entrepreneurship can help bridge the invention-innovation gap: a seamless fit with the clinical workflow, an initial focus on simple disease patterns, validity proof and a financial injection. Institutionally, the field-level characteristics on an individual level and wider system level are enabling for institutional entrepreneurship to occur. At an organizational level (inter-hospitals), more standardization is needed. Furthermore, establishing a favourable social position is key, by connecting to key opinion leaders and central players (manufacturers), and multiple embeddedness in both the data sciences field and medical field. Concluding, institutional entrepreneurship is likely to occur for tailor-made AI solutions. Future standardization on an inter-hospital level could provide opportunities for field-wide AI innovations.

ACKNOWLEDGEMENTS

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"Innovation is the ability to see change as an opportunity - not a threat."

— Steve Jobs

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List of abbreviations

AI	Artificial Intelligence
CE	Clinical Expert
IE	Institutional Entrepreneurship
FE	Flow cytometry Expert
IA	Innovating Agent
ICT	Information and Communication Technologies
MFC	Multi-colour Flow Cytometry
MRD	Measurable Residual Diseases
WSS	Wider System Stakeholder

1. Introduction

1.1 Relevance

As for any industry, the medical field has been flooded with data over the past years. Simultaneously, the field is facing the "data rich, information poor" problem; the exponentially growing volume of medical data is exceeding the human capacity to analyse these large and complex datasets (Radakovich et al., 2020). Thus, simply having access to more data does not necessarily lead to more knowledge. Artificial intelligence (AI) is expected to play a role in this. AI refers to any software or computer algorithm that mimics the human intelligence (He et al., 2019; Jiang et al., 2017). In its simplest form, the algorithms are programmed to solely perform tasks similar to the human actions (Frankenfield & Scott, 2021). They are unable to think beyond the predefined connections and cannot learn. However, the term also includes subsets with higher intelligence levels such as machine learning, neural networks, and deep learning[1].

Within the academic community, the innovative opportunities offered by AI in the medical field, referred to as clinical AI, have been an emerging topic. Clinical AI is expected to take a promising role in expanding the human capacity with functionalities such as diagnosis, treatment and clinical decision making (Jiang et al., 2017; Johnson et al., 2018; Steiner et al., 2020; Zini, 2005). It could for example play its role in precision medicine[2], speech recognition, understanding clinical documentation, surgical robots, and clinical decision support (Davenport & Kalakota, 2019). Academic researchers emphasized the potential of AI to increase accuracy and efficiency in de medical field (Kotter & Ranschaert, 2020; Patel et al., 2020).

From a societal perspective, AI holds a promise for the medical field in general, and in particular for the haemato-oncological field, referring to blood cancers. Cancer is the second leading cause of death worldwide, with a mortality rate of about 10 million per year (World Health Organization, 2021). Blood cancers account for about 10% of all new cancer diagnoses (Leukemia Research Foundation, n.d.). In haemato-oncological diseases, unravelling the heterogeneity between cells is key for accurate diagnosis and treatment. Major advancements in the field have led to high-throughput single-cell technologies such as flow cytometry, RNA sequencing or high-resolution microscopy (van Staveren, 2019). Currently, more than a thousand characteristics can be measured per hundreds to millions of cells. Detecting the relevant information in these large, multi-dimensional dataset remains a challenge (van Staveren, 2019). Even the most skilled expert can overlook patterns or deviations, which can have serious implications. AI algorithms can be trained to accurately recognize these patterns or deviations within seconds and can thereby prove to be the next step in improving patient survival rates. Therefore, AI could have a direct clinical impact and augment or even surpass the human analytic capacity in this specific field.

1.2 Problem identification and the gap in the literature

The problem we see, however, is despite the emerging academic interest in AI technologies, the real-world deployment in a clinical setting remains low (He et al., 2019; Kelly et al., 2019; Shaw et al., 2019; Steiner et al., 2020). In this thesis, this problem was referred to as the invention-innovation gap; *"invention is the process by which a new idea is discovered or created, while the adoption of an innovation is a decision to make full use of an innovation as the best course of action available"* (Rogers, 2003, p. 181). Thus, an invention refers to an idea, and an innovation refers to the successful

[1] For those unfamiliar with it: *Machine learning* is an algorithm that trains a machine how to learn. It can find hidden insights in data without being explicitly programmed where to look or what to conclude (Thompson, Li & Bolen, n.d.). *A neural network* is a type of machine learning inspired by the workings of the human brain. It refers to a computing system made up of interconnected units (like the neurons in the human brain) that processes information by responding to external inputs, relaying information between each unit. The process requires multiple passes at the data to find connections and derive meaning from undefined data. *Deep learning* is a subset of machine learning that enables computers to solve more complex problems. It uses huge neural networks with many layers of processing units, taking advantage of advances in computing power and improved training techniques to learn complex patterns in large amounts of data (Thompson et al., n.d.).

[2] Precision medicine refers to predicting what treatment options will most likely be successful for specific patients, based on the patient attributes and treatment context (Lee et al., 2018).

commercialization of that idea. This thesis examines the invention-innovation gap for AI developments in the haemato-oncological.

Previous empirical research has identified barriers for successful implementation of clinical AI. For example, He et al. (2019) pointed out that translating algorithms into clinical use is challenging due to the large amount of (standardized) data that is required, the integration in already established and complex workflows, and the compliance with regulatory arrangements. Serag et al. (2019) emphasized the need for a seamless fit into the clinical workflow, access to large data sets and the need for proper validation as key challenges. Furthermore, previous research has pointed out the complexity of technological innovation in hospital settings as it involves a large variety of stakeholders and organizational settings (Greenhalgh et al., 2004; Greenhalgh et al., 2017; Pope et al., 2013). Although previous research has identified barriers and facilitators, limited literature was found on *how* to overcome the problem. Consequently, no academic consensus was reached on how to bridge the invention-innovation gap yet. A need for further research to better understand and contextualize the translation of AI developments to clinical AI was expressed (Kelly et al., 2019; Radakovich et al., 2020; Shaw et al, 2019).

The identified barriers concern both the technology as well as the wider system. This is in line with one of the general understandings in the innovation sciences field: innovation does not happen in isolation. It is part of a wider system, with the institutional environment being a key element for the innovation system (Carlsson & Stankiewicz, 1991; Edquist, 1997). Institutions are defined as *"habits, routines and shared concepts used by humans in repetitive situations organised by rules, norms and strategies"* (Wieczorek & Hekkert, 2012 p. 76). More recent work pointed out that when new technologies do not fully match with existing institutions, institutional change should be prompted (Battilana et al., 2009; Hoogstraaten et al., 2020; Kukk et al., 2016). Thus, innovation is not only, nor predominantly, about technological changes, but also about actively seeking institutional change, needed to establish legitimacy and acceptance by the field.

Considering the above, the concept of institutional entrepreneurs caught attention, defined as "*actors who leverage resources to create new or transform existing institutions"* (Battilana et al., 2009, p. 68). As clinical AI is located at the intersection of the data sciences and medical field and incorporating algorithms for clinical application could transform the established standards, one can expect institutional entrepreneurship (IE) to be relevant for facilitating innovation. Battilana et al. (2009) reflected on the IE phenomenon, identifying enabling conditions for IE to emerge, and identifying how change subsequently happens. Taking the perspective that institutional change is as important as technological change, this thesis explored whether IE could be a strategy to help overcome the invention-innovation gap in the field.

Whilst the IE theory has widely been used in an organizational context, its application to the study of technology-related innovation has been limited to date (Hoogstraaten et al., 2020). Originally, IE is a broad theory that can be applied to a variety of empirical settings. Considering the technological nature of clinical AI however, IE could arguably benefit from an additional technology-related theoretical component. Moreover, given the complexity of the medical field, it might benefit from more specific empirical articulation. Therefore, the IE approach was complemented with domains of a framework that was specifically designed to study complex technologies in the medical field, namely the **N**on-adoption, **A**bandonment, **S**cale-up, **S**pread, **S**ustainability (NASSS) framework developed by Greenhalgh et al. (2017). The NASSS framework was designed to study failure of innovation in the medical field, examining seven domains with a holistic perspective on technological features, the internal capabilities of the agent and the contextual factors. The NASSS-framework is young, and Greenhalgh et al. (2017) strongly encourage other researchers to explore the applicability of the framework for different purposes and adapt it accordingly. Combining the two theories facilitated an institutional approach to technological innovation in the medical field.

1.3 Research aim and structure

The empirical aim of this thesis was to better understand and contextualize the invention-innovation gap for AI developments in the haemato-oncological field from an institutional perspective. To the author's current understanding, this had not been done before, thereby this thesis aimed to bridge a gap in the literature. The theoretical aim was to

strengthen the IE theory with components retrieved from the NASSS framework, making the IE perspective more applicable to technology-related innovation in the medical field. The societal aim of this thesis was to contribute to the value maximization of AI inventions for a clinical setting, making them clinically impactful.

This led to the following research question: ***What are the institutional facilitating factors and barriers for AI innovation in the haemato-oncological field, and could institutional entrepreneurship be a suitable strategy to help overcome the invention-innovation gap?***

To help answer this question, three sub-questions were formulated based on the more in-depth features of the theoretical approach, extensively described in section 2. *(1) What are the relevant technology-related elements? (2) What are the key field-level characteristics in the haemato-oncological space? (3) How does the actor's social position influence the perception of the field?* Sub-question (1) helped to understand the case-specific technological elements. Sub-question (2) and (3) gave insights into the factors influencing the likeliness of agents to position themselves as institutional entrepreneurs. Connecting all questions allowed us to answer the main research question.

In this research, the questions were explored in the context of AI in the haemato-oncological field, where there is a direct need for supporting the human analytic capacity. The research followed an interview-based, qualitative process. A single case was used, represented by FlowView Diagnostics, an early-stage Dutch start-up developing AI for accurate and fast monitoring of the data of blood cancer patients. The company is quickly moving on the invention-innovation path, currently focusing on the Dutch market as a starting point. The focus of this research was the algorithm of FlowView Diagnostics, and learnings were extrapolated to the broader field of clinical AI in the haemato-oncological field. Therefore, the unit of analysis was the algorithm of FlowView Diagnostics, the scope of this research was AI developments in the haemato-oncological field in the Netherlands.

This thesis was structured as follows. Chapter 2 elaborated on the theoretical embedding of the research, followed by the integrated theoretical framework that was used throughout the research process. Chapter 3 addressed the methodology that was followed to conduct the research. Subsequently, the empirical findings were presented in chapter 4. Chapter 5 analysed the key findings, which were concluded upon in chapter 6. Chapter 7 discussed the limitations, contributions, future research suggestions and presented the management implications for FlowView Diagnostics.

2. Theory

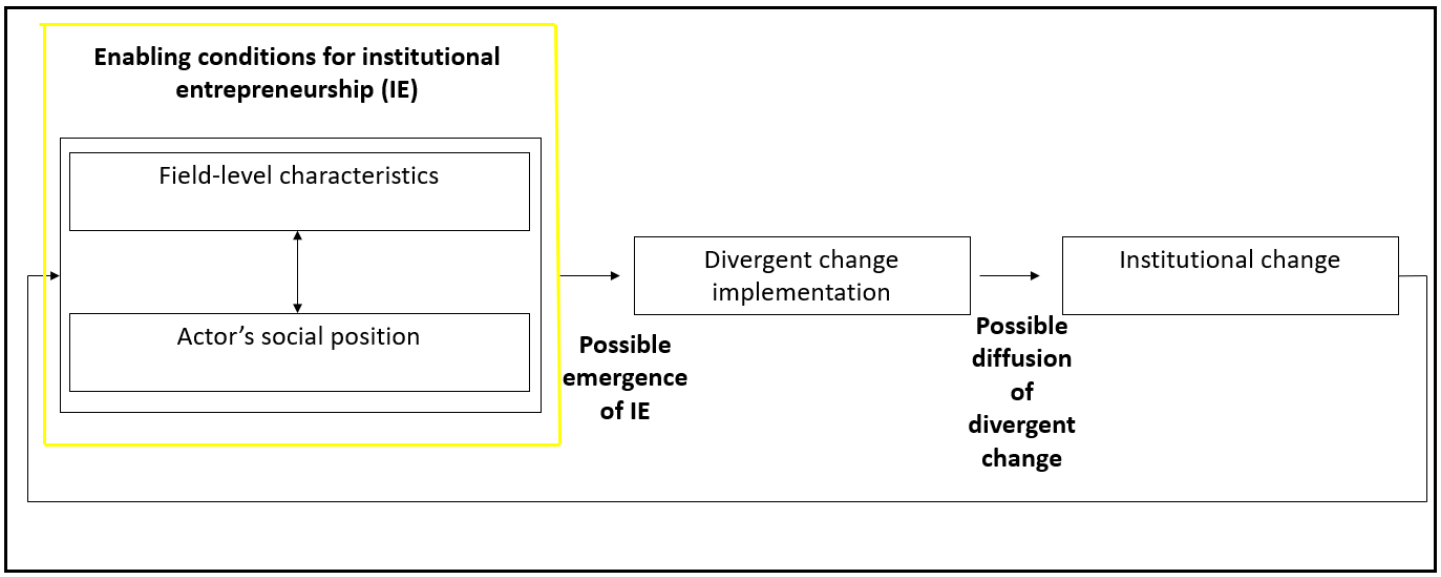
This research was built on the institutional entrepreneurship (IE) theory of Battilana et al. (2009), providing insights into how change happens at an institutional level. Considering the technological nature of clinical AI and the complexity of the medical field, the IE perspective was complemented with domains of the Non-adoption, Abandonment, Scale-up, Spread, Sustainability (NASSS) framework developed by Greenhalgh et al. (2017), designed to study failure of technological innovation in the medical field. By integrating the two, the IE perspective was contextualized for technological innovation in the medical field. Subsections 2.1 and 2.2 extensively describe each theory, its strengths, and limitations. Subsection 2.3 presents the integrated framework, used to guide this research.

2.1 Institutional Entrepreneurship

Institutional theories are a central stream within organization studies, focussing on the relationship of agents, being individuals or organizations, and the fields they operate within. Traditionally, institutional theories highlight how 'fixed' institutions guide the daily decisions and behaviour of individuals (Battilana et al., 2009; Tonoyan et al., 2010). They focus on determinism and stability (Leca & Naccache, 2006). To repeat, institutions were defined as *"habits, routines and shared concepts used by humans in repetitive situations organised by rules, norms and strategies"* (Wieczorek & Hekkert, 2012 p. 76). The medical field is generally perceived as highly institutionalized. Innovation in the field mostly involves strict regulatory processes and requirements, to ensure safety and quality. The emergence of AI technologies indicates a new era in the field. Consequently, it can be expected that the implementation of clinical AI will requires changes of established standards in the field. For example, routines might change, roles might change, and a basic understanding of data sciences might need to become part of a clinical expert´s literacy. As stated by Battilana et al. (2009, p. 78), "*implementing change that builds on existing institutions is challenging, implementing change that breaks with existing institutions more so"*. A better understanding of institutional change in the haemato-oncological field can be crucial for a better understanding of the invention-innovation gap.

Reforming institutions is paradoxical within the tenets of the traditional institutional theories. The question of how actors, whose beliefs and actions are determined by existing institutions, can break with these very same institutions, and innovate, is often referred to as the *paradox of embedded agency*. More recent literature within institutional studies has focussed on the role of agency within the institutional context, instead of the determining institutional context. Within this new stream, the concept of institutional entrepreneurship (IE) emerged. Institutional entrepreneurs consider simultaneously the influence of both an actor´s actions and the structures in which they are embedded, without conflating them; they travel the difficult road that passes between a rational choice model of agency on one side and structural determinism on the other (Leca & Naccache, 2006; Mutch, 2007; Thornton & Ocasio, 2008). It highlights the actor´s ability to influence the 'fixed' institutions through leveraging critical resources (Battilana et al., 2009; DiMaggio, 1988; Garud et al., 2007). The paper of Battilana et al. (2009), *"How Actors Change Institutions: Towards a Theory of Institutional Entrepreneurship",* became arguably one of the most influential papers on IE, being cited 977 times in Web of Science in May 2021. Institutional entrepreneurs were actors leveraging resources to create new or transform existing institutions. This is independent of the initial intent of the actors, and whether the creation or transformation has been successful. These actors can be organizations or individuals (Battilana et al., 2009). Clinical AI lays at the intersection of the data sciences field and the medical field, both having their individual institutional environment. The introduction of clinical AI might therefore conflict with existing established institutions, an adapted or even new institutional environment needs to be created. In the aim of studying the invention-innovation gap and in the assumption that institutional entrepreneurs seek institutional change to establish innovation, it should be examined *whether* IE is likely to occur in the field, and/or what is needed to enable IE to occur. The research of Battilana et al. (2009) theorized on enabling conditions for IE to occur, how change is implemented and how institutions consequently can be changed. This research explored whether actors are likely to act as institutional entrepreneurs, therefore, solely the enabling conditions were studied (see *figure 1*). Battilana et al. (2009) identified field-level characteristics and the actor's social position as two interacting key categories of enabling conditions for IE to emerge, further explained below.

Figure 1: *The full cycle of institutional entrepreneurship leading to institutional change, proposed by Battilana et al. (2009). The figure was adapted to highlight the focus of this thesis, which was solely the first part of the process.*



2.1.1 Field-level characteristics

Battilana et al. (2009) identified two main field-level characteristics that can enable IE: the heterogeneity of institutions and the degree of institutionalization. *The heterogeneity* of institutional arrangements in a field refers to the variance in characteristics of different institutional arrangements. Heterogeneity is likely to give rise to institutional incompatibilities that become a source of internal contradiction – a pair of features that together produce an unstable tension in a given system. Actors exposed to contradictory institutional arrangements are less likely to take existing arrangements for granted and more likely to question and possibly diverge from them. *The degree* of institutionalization refers to how strictly embedded the institutions are. Lower degrees are associated with higher levels of uncertainty in the institutional order, which might provide opportunities for strategic action and vice versa. IE could facilitate change in the field, consequently, help an invention to become an innovation. By investigating how the clinical AI field for haemato-oncological is organized, it can be explored whether the field-level characteristics are favourable for IE to occur. It is assumed that high levels of heterogeneity and low degrees of institutionalization are associated with IE.

2.1.2 Actor´s social position

In a setting where field-level characteristics encourage IE, only some actors will exploit the opportunity. Battilana et al. (2009) suggested that the social position an actor occupies in an organizational field plays a particular role in this. The actor´s social position reflects the relation the actor has to its environment and might affect the actor´s perception of a field, perception of legitimacy and access to resources (Battilana et al., 2009). Its position within as well as across fields influences the likelihood that individual actors will engage in IE.

There is no consensus on a general optimal enabling position *within the field*. Early studies point out that divergent change is more likely to be initiated by low-status organizations (Garud et al., 2002; Hirsch, 1986; Kraatz & Zajac, 1996; Tushman & Anderson, 1986), which are said to be at the periphery of a field. In contrast, other studies found such change being initiated by high-status organizations (Greenwood et al., 2002; Sherer & Lee, 2002). The optimal position depends on the institutions from which they diverge and is dependent on the case-specific context. To facilitate IE, the optimal social position should be identified.

Regarding the social position *across fields*, it is suggested that the intersection between fields is more likely to spawn IE (Phillips et al., 2000; Rao et al., 2000). Being involved in multiple fields was referred to as multiple embeddedness, allowing to transpose key elements from different fields and resonate them with the involved fields. The institutional entrepreneur should look for a common ground and frame discourses that resonates with the interests and values of all stakeholders (Fligstein, 1997; Greenwood et al., 2002; Hsu, 2006; Suddaby & Greenwood, 2005).

2.1.3 Strengths and limitations

IE is a powerful and mature theory when it comes to considering institutions hampering and/or facilitating change. The approach carefully considers the enabling contextual factors intending to create a favourable environment for change to occur. Clinical AI currently underperforms in translating from invention to innovation. IE might serve as a relevant strategy to facilitate innovation. Studying the enabling conditions in the field explores whether the field is, or can be, ready for IE to emerge.

In the context of this thesis, two limitations were pointed out. Firstly, the IE theory emerged from organizational studies and initially focuses on organizational change, which does not necessarily involve technological change. It might be argued that the IE theory lacks a technological component when applying it to technology-related innovation. Hoogstraaten et al. (2020) reviewed 140 articles on IE and found that only 27% focussed on technological innovation, with especially little attention given to digital innovation. Secondly, the theory provides a strong overarching view on change, offering theoretical concepts that apply to wide empirical settings, being valuable to understand change dynamics in general. When applying the theory to the medical field, known for its complex structure, it might lack empirical articulation.

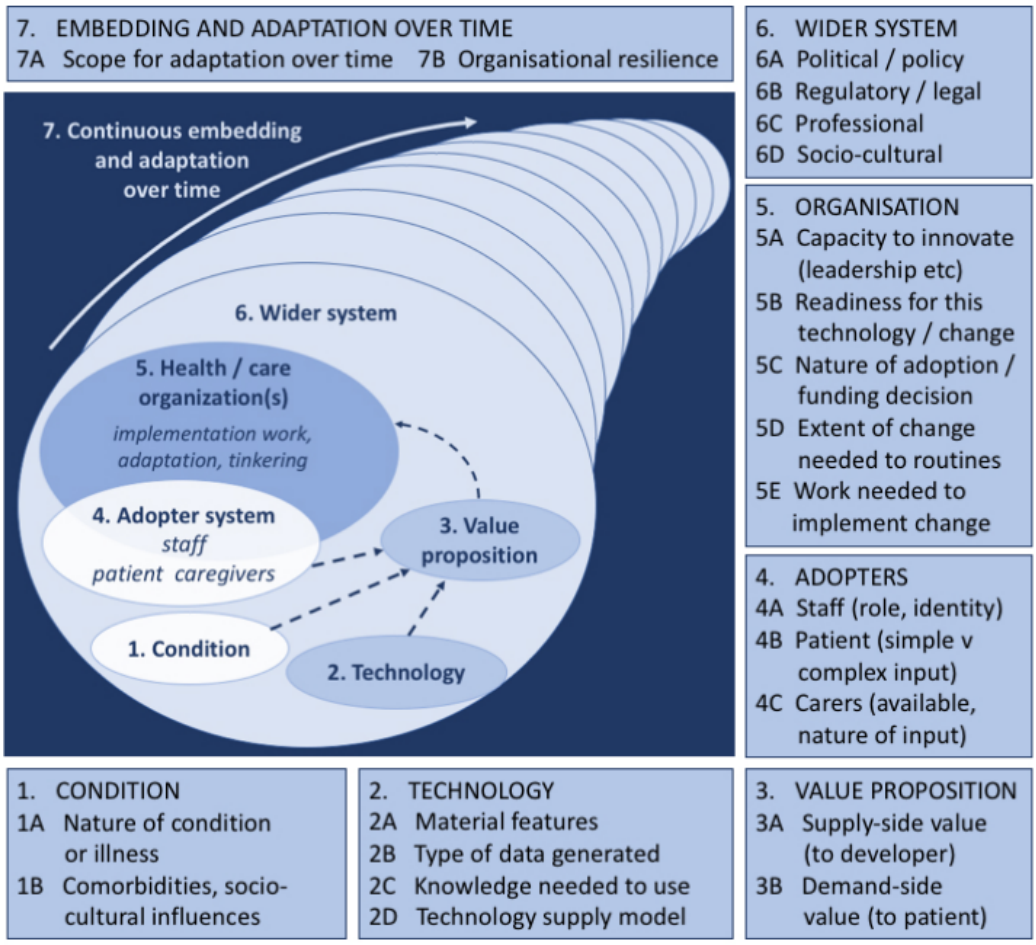
To account for these limitations and make the theoretical approach more applicable to technological-related innovation in the medical field, the IE perspective was complemented with domains of the **n**on-adoption, **a**bandonment, and challenges to the **s**cale-up, **s**pread and **s**ustainability (NASSS) framework, developed by Greenhalgh et al. (2017).

2.2 NASSS-framework

The NASSS framework has been developed by Greenhalgh et al. (2017) to study complex technologies in the health sector. It addresses the Non-adoption and Abandonment of technologies and the challenges associated with moving from a local demonstration project to one that is fully mainstreamed and part of business as usual locally (Scale-up), transferable to new settings (Spread), and maintained long term through adaption to the context over time (Sustainability). The framework is an evidence-based, pragmatic framework to help predict and evaluate the complex technologies in the healthcare sector. For example, it has recently been applied to study AI innovation in radiology in the study of Strohm et al. (2020). The framework presents seven domains (see *figure 2*) that should be evaluated: the condition or illness, technology, value proposition, the adopter system (comprising professional staff, patient, and lay caregivers), the organization(s), and the wider institutional and social context. Some of the NASSS-domains were used to specify the IE approach to the specific case of clinical AI in haemato-oncological.

The condition or illness deals with the clinical context in which the innovation will be implemented. It addresses the nature of the illness and elements such as comorbidities of patients. These elements can differ per condition. The condition should be well understood to define the suitability of the technology. Haemato-oncological diseases is an umbrella term for various conditions, all having their individual disease patterns. For the IE analysis, it is therefore relevant to explore whether all disease patterns within the field would be suitable for the application of clinical AI, and what factors of specific conditions are important to consider. *The technology* considers the technological features of a technology, impacting the usability, appropriateness, and dependability of technologies. Moreover, the relevant knowledge bases to support and use the technology should be considered. The technological features of clinical AI might be new to the experts in the medical field, and the medical requirements might be new to data scientists. Attention should be given to creating the right fit. This furthermore requires identification of *the value proposition,* which concerns whether the technology is worth developing and for whom it generates value. The value proposition can be split into an upstream and downstream value proposition. The first concerns the supply-side logic of financial markets and investment decisions. The latter concerns the demand-side logic of health technology appraisal, reimbursement, and procurement. *The adopter system* refers to the (continued) adoption or non-adoption reasons and acceptance of the technology. This domain studies staff, patients, and caregivers, thus, on an individual level. Overarching the individual reasonings, the adopter system is embedded in an organization. *The organization* refers to the organization's capacity and readiness to take up a specific technology, in the case of clinical AI being the hospital or laboratory. Rationales for the decision to allocate budget to the specific technology are key. Also, the extent to which work routines will be disrupted by the new technology and the work involved for implementation are key to consider. *The wider system* refers to the wider institutional and sociocultural context surrounding the organizations. For example, health policies, fiscal policies and the position taken by professional bodies and defence societies, and legal and regulatory aspects of the technology. As the medical field is generally perceived as strictly organized, it is relevant to study the wider system context for an emerging field. The framework thus present three levels – the adopter system, the organization, and the wider system - of the medical field, all proved to be relevant to study innovation failures. Therefore, all three levels should be considered in the institutional approach. Lastly, *embedding and adaptation over time* assesses the ability to continuously adapt the technology. Any technology is inextricably interlinked and dynamically evolving, often against a rapidly shifting context.

Figure 2: *The NASSS-framework by Greenhalgh et al. (2017).*



2.2.1 Strengths and limitations

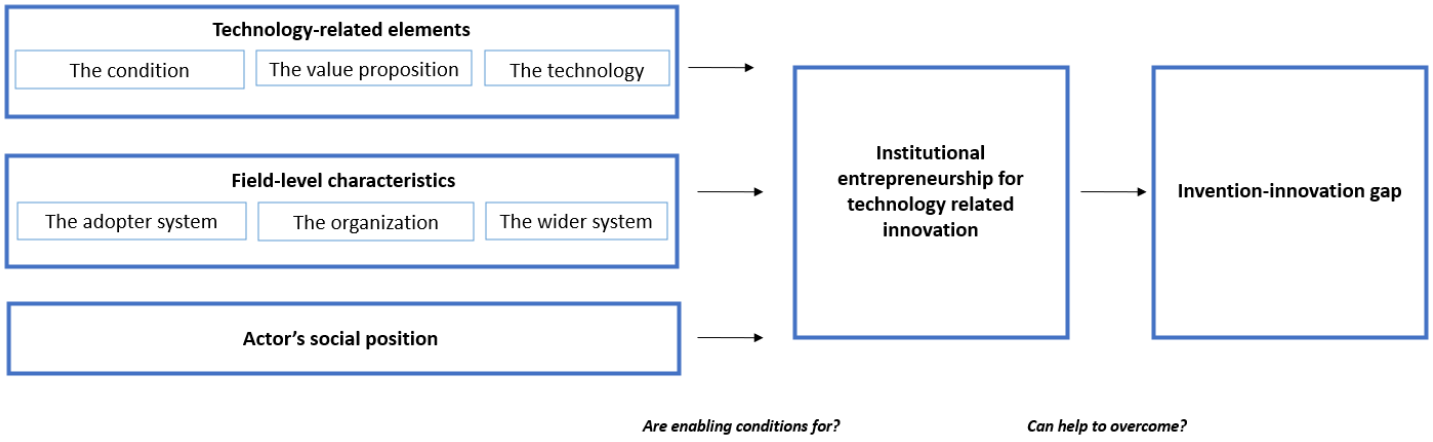
The NASSS framework is relatively young. Whilst the framework is taking off to be widely applied, few academic publications have been made. Greenhalgh et al. (2017) strongly encourage other researchers to explore the applicability of the framework for different purposes and adapt it accordingly. The key strength of the framework is that it offers an evidence-based, holistic framework that identifies domains hampering, or facilitating, innovation. A limitation of the NASSS-framework is however that this functional framework does not have one specified, overarching theory behind it.

2.3 Integrated theoretical framework

An integrated theoretical framework (see *figure 3*) was built, based on the identified and case-specified strengths, limitations, and expected synergies of the IE theory and NASSS framework. It allowed an institutional perspective on complex technological innovation within the medical system and was used to guide this research.

The NASSS framework provided domains on the technology-related component to the extent that it considers the condition, the technology, and the value proposition. They are expected to give information on technological prerequisites for the innovation, establishing a technological proposition for which acting as an institutional entrepreneur might be fruitful. Adding these as a new building block "technology-related elements", the first limitation of the IE theory is accounted for. Furthermore, the NASSS framework indicated the adopter system, organization, and the wider system as levels in the field, which were used to guide the empirical articulation for the field-level characteristics. Integrating these levels as focus areas consolidated the second limitation of the IE theory. The integrated framework also complements the beforementioned limitation of the NASSS framework, as the overarching perspective of change is in the core focus of the IE perspective. Consequently, it is expected that the two perspectives synergize each other[3]. This leads to the integrated theoretical framework with three main building blocks being the technology-related elements, the field-level characteristics, and the actor´s social position. Assessment of these building blocks was used to provide insights on enabling conditions for IE to occur in the context of technology-related innovations in the haemato-oncological field. This indicated the opportunities for IE to occur, which could potentially be a strategy to help overcome the invention-innovation gap. The framework thereby facilitated an institutional perspective on the invention-innovation gap for the specific case. The use of this framework is explained in *section 3, Methodology*.

Figure 3: *Integrated theoretical framework: The enabling conditions for institutional entrepreneurship in the context of technological change in the medical field. The framework is based on the theory of Battilana et al. (2009) and Greenhalgh et al. (2017).*



[3] The NASSS-domain "embedding and adaptation over time" is not shown in the integrated framework, as it is not considered a specification of the IE approach nor a technological component, which was the purpose of the integrated framework.

3. Methodology

This thesis theoretically aimed to explore the integrated framework for the specific context of clinical AI in the haemato-oncological space. Thereby, it aimed to evaluate the enabling conditions for institutional change in technology-related innovations, to potentially contribute to bridging the invention-innovation gap. Building on the integrated theoretical framework (section 2.3), the enabling conditions for institutional change in clinical AI developments were explored using a single case study, further explained in 3.1. This is followed by the explanation of the research design in 3.2. After that, data collection and the analysis strategy are elaborated upon in 3.3. Lastly, the research quality measurements are discussed in 3.4.

3.1 Case selection – FlowView Diagnostics

FlowView Diagnostics was selected as an appropriate case to study the research problem of this thesis: the company presents an AI invention coming out of the academic community, currently travelling the path towards becoming a clinical AI innovation in the haemato-oncological field. It aims to facilitate more accurate and faster monitoring and diagnosis of blood cancer patients.

FlowView Diagnostics is a for-profit, early-stage start-up, developing an algorithm that enables more accurate and faster monitoring of minimal, or more appropriately, measurable residual diseases (MRD) in blood cancers. MRD is used to describe a very small number of cells (<.001%) that remain in the body during or after treatment, which is common in blood cancers (National Cancer Institute, 2020). The patient is said to be in remission when no cancer cells can be detected in the blood and there are no symptoms. These remaining cells might or might not lead to a relapse of the disease, however, it is quite common for blood cancers such as (acute) leukaemia[4] and multiple myeloma[5] to relapse after an initial remission. The MRD value positively correlates to the risk of relapse for various types of blood cancers, therefore, accurate monitoring is crucial (van Staveren, 2019). To further contextualize, the general diagnostic process of blood cancers and the relapse scenarios can be found in *Appendix 1*.

Currently, multi-colour flow cytometry (MFC) is a standard diagnostic tool being used for diagnosing cancer cells in the patients' bone marrow. For those unfamiliar with MFC, an in-depth description of the technology is provided in *Appendix 2*. In summary, MFC is a method for analysing cell characteristic with high sensitivity: it can detect up to one divergent cell amongst one million normal cells. Advancements in this technique have led to the possibility of measuring dozens of characteristics per individual cell, providing large volumes of raw data. The crowded data output is currently manually interpreted by the expert for diagnosis and monitoring. Translating the data into relevant information requires lots of expertise, time, and experience. Moreover, the process is restricted to the availability of clinical expert and presents risks of human biases and errors.

As a reaction to this problem, researchers of the Radboud University and the University Medical Centre Utrecht developed an algorithm that can analyse the large volumes of raw data produced by the MFC and represents the findings as a simplified 2D-image. The algorithm filters out all the normal cells, leading to a non-crowded representation of the malignant cells only. Consequently, interpretation requires less expertise, less time and is trained to detect early indications of relapse. The algorithm can detect connections that outperform the conventional method. Moreover, the algorithm is expected to compensate for the human error, decreasing the number of false negatives. Additionally, it can

[4] Leukaemia is a non-solid cancer that develops in all lineages of blood cells and starts in the bone marrow and travels through the bloodstream. The bone marrow produces mutated cells and spreads them in the blood, where they crowd out healthy blood cells. Leukaemia occurs in many different forms, however, the two main diagnoses are acute or chronic, the first being more aggressive. The global age-standardized incidence rate is lays between 4.5 (females) and 6.3 (males) per 100 000 inhabitants (International Agency for Research on Cancer, 2020a).

5 Multiple myeloma is a cancer that develops in plasma cells in the bone marrow. Plasma cells normally produce antibodies that attack infections and diseases. When plasma cells become cancerous, they accumulate in the marrow and damage or weaken bone and cause pain. Cancerous plasma cells also produce faulty antibodies, which complicate the ability for the body to fight infections. The global age-standardized incidence rate is lays between 1.5 (females) and 2.2 (males) per 100 000 inhabitants (International Agency for Research on Cancer, 2020b).

be run 24/7 and can detect malignant cells to a similar depth of the conventional methods. The algorithm can be designed for all steps and complexities of disease patterns, its main added value is the simplification of the resulting output. Ideally, it allows for faster detection and more accurate monitoring of the data, thus of the patient.

A patent on the method was granted in 2015 to the Radboud University and University Medical Centre Utrecht as shared patent holders and forms the basis of FlowView Diagnostics. An external CEO with market expertise in the digital medical field was onboarded, and the inventors are involved in the company in an advisory role for their technical expertise. The company was officially founded in April 2020. Currently, the source code of the algorithm is finished and already tested in patient samples. The Graphical User Interface is yet to be developed. The clinical validation of this decision support algorithm will follow. If the financial situation allows for it, further research activities will be established by the RU and University Medical Centre Utrecht. The algorithm of FlowView Diagnostics aims to quickly travel the path from AI invention towards innovation in the haemato-oncological space.

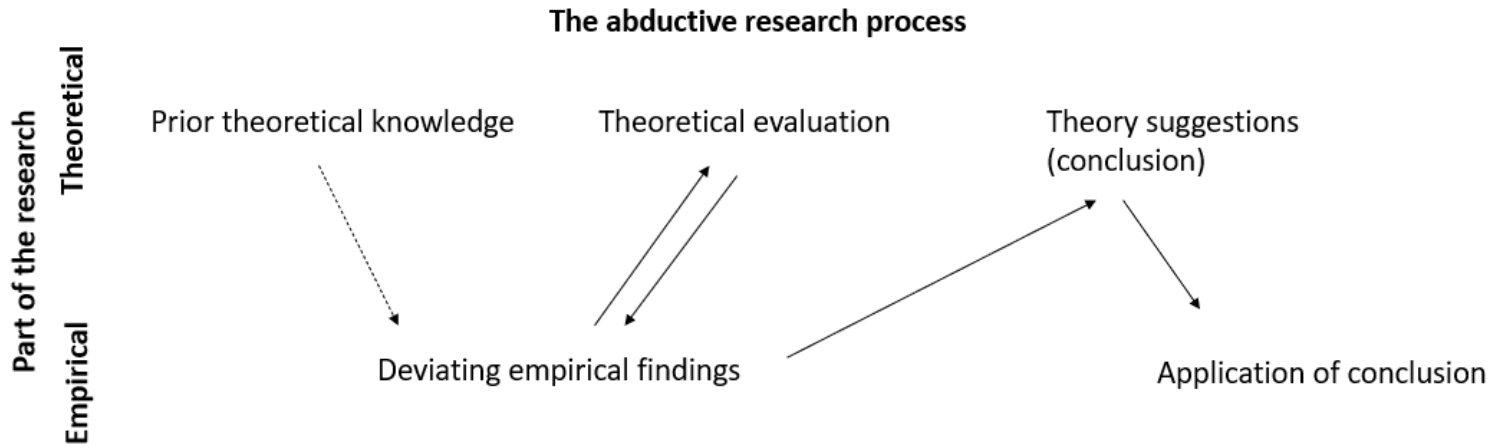
FlowView Diagnostics was selected as it is an appropriate case to study the research question: the company started in the academic community as a research interest and is now quickly moving along the invention-innovation path while key components of this promising invention, such as the graphical user interface, are still to be shaped. Researching the institutional environment with an additional focus on the technology-related elements, will contribute to new theoretical and practical perspectives and can in parallel help FlowView Diagnostics to successfully continue the development-to-implementation process. The careful selection of an appropriate research design and approach in which the case was embedded allowed us to extrapolate findings to what they mean for AI innovations in the haemato-oncological field in general.

3.2 Research design

Considering both the theoretical and empirical aim of this thesis, a case study design was most appropriate. Case studies are a suitable strategy when the research aims to deepen the understanding of a phenomenon in a real-life setting (Bryman, 2016). In this thesis, a single case was selected – FlowView Diagnostics – offering an excellent representation of the problem studied in this thesis. Single cases explicitly allow for a deep and nuanced understanding of previously understudied phenomena, they can be highly informative and meaningful (Boddy, 2016; Dyer & Wilkins, 1991). They are used to verify old theoretical relationships and explore new ones (Gustafsson, 2017). In the aspiration of contextualizing and creating a better understanding of the invention-innovation problem, combined with the aim of exploring the enabling conditions of IE in an understudied context, a single case study design seemed suitable. Accompanying a single case study design, a qualitative research method was most appropriate. Qualitative research is mostly used to gain an in-depth understanding of phenomena (Boddy, 2016); it is more concerned with words than numbers (Bryman, 2012).

This thesis intended to elaborate on prior theoretical knowledge. It aimed to strengthen the IE approach by complementing it with domains retrieved from the NASSS framework. Considering the aims of this thesis, an abductive approach appeared suitable. Abductive research is concerned with the particularities of specific situations where deviations from general patterns are essential. It enables 'systemized' creativity to develop new knowledge (van Hoek et al., 2005). It allows for the constant interaction between empirical and theoretical findings. Moreover, an abductive approach is common for case studies (Van Hoek et al., 2005). In this thesis, the research question was formulated based on existing theoretical literature, and the investigation of the questions was done using an in-depth case study while remaining open to new findings. The integrated framework (section 2.3) was used as a guideline, of which the operationalization is described and presented later in the next subchapter. As the integrated framework has not been used before, findings were iteratively evaluated with the proposed theoretical approach. The last part of this research concluded on theoretical additions or proposed changes and applied the suggested theory to the case. *Figure 4* presents a visualization of the abductive research process.

Figure 4: *Visualization of the abductive research approach, based on the work of van Hoek et al. (2005).*



3.3 Data collection and data analysis

The term clinical AI brings together multiple established fields and includes a range of expertise, while various application areas, technologies and functional stakeholder groups can be represented by different players in the field. Therefore, prior to collecting data, a deeper understanding of contextual information on the general diagnostic processes in the field and the flow cytometry technology was needed. Contextual information was collected through an internship at FlowView Diagnostics, informal expert conversations and by attending 10 expert events. Whenever relevant topics were discussed, notes were taken. Contextual information is presented in *Appendix 1 and 2*, and an overview of all attended events can be found in *Appendix 3*.

Furthermore, prior to collecting data, the key stakeholder groups in the field were defined. This was of importance for the representability of the findings and was based on the contextual activities as described above. Four groups were identified: the flow cytometry experts (FE), the clinical experts (CE), the innovating agents (IA), and the wider system stakeholders (WSS). A description of their functionalities can be found in *table 1*. The patients were no key stakeholder group, as they are no direct user of the data interpretation software. Including all key stakeholder groups in the data collection process was important to get a holistic view of the institutional dynamics in the field.

Table 1: *Description of the key stakeholder groups for AI in the haemato-oncological field.*

Key stakeholder group	Description
Flow cytometry expert (FE)	Responsible for data interpretation of the data provided by the flow cytometry analysis. This is for example the immunologist of clinical chemist.
Clinical expert (CE)	Defines the diagnosis and treatment options for the patient, based on the interpretation of the flow cytometric expert.
Innovating agent (IA)	The individual or organization bringing the innovation forward. This group also includes software developers.
Wider system stakeholder (WSS)	This group includes key stakeholders of the system surrounding the innovation. Stakeholders such as medical insurance companies, regulatory experts, IT managers at hospitals and flow cytometry manufacturers should be considered.

An operationalization table was designed in advance (see *table 2*) to guide the data collection process and analysis. This table was based on the concepts of the integrated framework, guiding the data collection and analysis process to be able to answer the research questions. The table starts with the key concepts and domains of the integrated framework, which are specified in elements, according to the theory review (described in chapter 2 of this thesis). The identification of elements facilitated the formulation of questions, which made the domains and variables measurable. It subsequently allowed to explore the dynamics between the domains and translate them into what they mean for possibilities for IE.

Table 2: *Operationalization table.*

Enabling conditions for institutional entrepreneurship in technology-related innovation			
Concept	**Domain**	**Element**	**Questions**
Technology-related elements			
Condition	Nature of condition	Suitability for technology	What is the nature of haemato-oncological diseases?
Value Proposition	Value Proposition	Downstream	Do you think the data provided through flow cytometry can be presented more intuitively? If yes, how?
		Upstream	

			Should all the data be always represented? What features are crucial for an AI system in the field? What is the improvement that you are ideally looking for?
Technology	Features	Material features	What are the key features of the technology? Do you think the staff should go through any training processes to learn how to use an algorithm? Why? What knowledge is required to use the technology? What kind of knowledge does this innovation bring into play? What is key for the technology supply model?
		Knowledge generated	
		Knowledge to use	
Field-level characteristics			
Heterogeneity of institutions & Degree of institutionalization	Adopter system	Users	How and why do you use MFC or MRD data? What elements of the data are most important?
	Organization	Capacity and readiness to innovate	What does the workflow look like? Do you expect any difficulties acquiring financial support for implementing this software? If yes, what kind? How important is it for your organization that the innovation has an appropriate regulatory and privacy protection compliance in place? Do you think the requirements are adequate at the moment?
		Ease of adoption decision	
		Clinical workflow	
	Wider system	Political context	Is the way of diagnosing MRD strictly regulated? Are there any alternatives that you are aware of? Are there other contextual factors that might hamper or facilitate the usage of new algorithms?
		Regulatory system	
		Professional bodies	
Actor's social position			

Perception	Field	Legitimacy requirements	Would you rather be open-minded or sceptical towards implementing AI in the field? Why? What is key to consider a new technology for flow cytometry/ MRD diagnosis as legit?
		Attitude on AI	

Data was collected by conducting semi-structured interviews. Semi-structured interviews provide the interviewer with in-depth qualitative data. They enable interviewees to provide detailed information while leaving the opportunity for complementary factors to arise. Semi-structured interviews created the possibility for concepts to emerge from the data (Bryman, 2016). The interview questions were derived from the questions in the operationalization table and were used as guidelines for the conversations. Two pilot interviews were conducted with a flow cytometry expert that was familiar with the research and the case, to test the flow of the interview, to improve the formulation of interview questions and to guide redesign, until interview outputs were sufficiently useful to research this thesis. The content was not used as findings. Consequently, an interview guide with all interview questions was designed, providing an appropriate set of questions to study the variables of the integrated framework. For each interview, questions had a personalized framing and selection of the questions to keep them motivated to share information, based on the expertise and knowledge base of each interviewee. For example, a flow cytometry expert was approached with a focus on flow cytometry, a clinical expert was approached with a focus on the disease type. The full interview guide can be found in *Appendix 4*.

To enable findings to be representable to the field, specific attention was given to include interviewees of all key stakeholder groups. This was important as preliminary research indicated that interconnectivity and interdependence of the relevant stakeholder group are crucial for correctly understanding and contextualizing the system. The network of FlowView Diagnostics' project team was used as a starting point for the purposive sampling of interviewees, reaching all key stakeholder groups. This was followed by snowball techniques to expand the interviewee selection until data saturation was reached. This means that towards the end of data collection, repetitive answers were given (Bryman, 2016). Specific attention was given to include stakeholders connected to several hospitals, either academic or peripheral, to prevent professional biases. The full data collection contained 18 interviews, each lasting 63 minutes on average. In sum, this provided the researcher with 1132 minutes of interview information. A minimum of 4 interviewees per stakeholder group was included. An overview is provided in *table 3.*

Table 3: *An overview of the number of interviews per subgroup and stakeholder group.*

Stakeholder group	**Subgroup**	**# of interviews**
Flow cytometry expert		**5**
Clinical expert		**4**
Innovating agent	IT	1
	Regulatory	1
	CEO	1
	FE	1
	Subtotal	**4**
Wider system stakeholder	Manufacturers	2
	IT	1
	Digital innovators	2
	Subtotal	**5**
Total		**18**

Information on the data handling and topics to be discussed were shared with the interviewee in advance. Permission was asked to use the collected data and to record the interview. When recording was not permitted (in 4 interviews), notes were taken as complete as possible. The interviews were conducted either face-to-face or by video-call, and were all in English or Dutch, depending on the preference of the interviewee. For data handling, interviewees were referred to as their stakeholder group and number, for example, the first flow cytometry expert was referred to as flow cytometry expert 1 (FE1). A full overview of all interviewees, interview format and duration can be found in *Appendix 5*. In parallel with the data collection, informal expert conversations took place with interviewees and 10 events were attended (see *Appendix 3*) to, besides contextualization through which descriptive and conceptual gaps were filled, cross-verify remarkable statements of interviewees which facilitated data triangulation.

After data collection, the data was prepared for analysis. Each interview was transcribed within 48 hours. This was important to capture as many impressions as possible. Data was processed using the qualitative data analysis computer software package 'QSR Nvivo'. A coding scheme was derived based on the operationalization table and the interview guide. A-priori coding was used according to this scheme, to relate all collected data to the research question. Where a-priori codes were no good fit, new codes were created, allowing new concepts and potential theoretical contributions to emerge. After initial coding, the analysis was refined with a more grounded approach within the coded items, to keep the explanation of the indicators close to the terminology that was used by interviewees. The initial coding scheme can be found in *Appendix 6*, the final coding scheme with examples of how it was operationalized in *Appendix 7*.

Subsequently, the data sorted by codes were examined according to the operationalization table, evaluating, elaborating, and adapting the integrated framework. Examination per element allowed to answer the research sub-questions. After examination, the dynamics between the concepts were explored and translated into insight for the field. This allowed to formulate an answer to the main research question, and additionally, to provide empirical, theoretical, and practical insights on the invention-innovation gap. Completing the abductive research process, the findings were applied to the case.

3.4 Research quality

When conducting qualitative research, reliability and validity are two prominent research quality indicators that should be reviewed (Bryman, 2016). To ensure the quality of the findings of this thesis, these two indicators were closely considered.

The reliability of a research reflects the consistency of the study (Bryman, 2016). By conducting pilot interviews to verify the interview guide, and starting the transcription process as soon as possible after the interviews, the reliability of the study is reinforced. In both data collection and analysis, the operationalization table and coding scheme were closely followed. To anticipate possible personal bias during this process, peer discussions and feedback sessions with the supervisor were held. In addition, an intercoder reliability check was done using Fleiss' kappa in SPSS Statistics. This is an inter-rater agreement measure to determine the level of agreement. Two Innovation Sciences researchers each labelled 25 statements of the database, to check for potential deviations. The verification resulted in an Alpha of 0,828, which can be considered reliable (>0.8). An overview of the full reliability check can be found in *Appendix 8***.**

The validity concerns whether a concept measures that actual concept. Validity can be internal and external. Internal validity refers to whether an indicator assigned to measure a concept, is measuring the intended concept, while external validity refers to whether the findings can be generalized (Bryman, 2016). To ensure internal validity, interviews were conducted closely following the interview guide and data was processed following the strict coding rules. Constant comparison was made between findings and theoretical concepts, to ensure the intended concepts were measured. Following the abductive research approach, where theoretical elaborations were suggested, this was verified with additional empirical findings. Findings were formulated remaining as close as possible to the original words of the original data, to avoid inconsistencies. As argued for in chapter 3.2, findings were triangulated by assuring multiple interviews per stakeholder group and by cross-verifying remarkable statements through attended events and informal expert conversation. With regards to the external validity, the contextual particularities of a single case study caused that findings could only limited be extrapolated to the wider field. To partly account for this, interviewees with variety in experiences, functionalities and relations to the specific case, and the wider field, were selected. Furthermore, the attended expert events were used as an indication of whether findings were also representable in the wider field. Events were selected based on the topic and the speakers or organization. A full overview can be found in *Appendix 3*. During attendance, notes were taken proactively.

4. Findings

This chapter presents the findings of the research per element of the operationalization table. Following the abductive approach, adaptations in domains were made according to the empirical findings, to make the theory better applicable for the research problem and the scope of this thesis. Firstly, the technology-related elements (4.1) were examined. Thereafter, the enabling conditions for IE – the field-level characteristics (4.2) and actor´s social position (4.3) - were examined. Subsequently, the dynamics between the concepts were analysed and linked back to the theory in chapter 5.

4.1 Technology-related elements

The technological-related elements were concerned with the prerequisites of any AI innovation in the field, necessary for a technology to come to a point where IE can emerge. Three domains were discussed as technology-related elements: the condition, the value proposition, and the features of the technology. Key findings are presented in *table 4* and extensively discussed below.

***Table 4**: Summary of findings of the technology-related elements.*

Element	Domain	Key finding
4.1 Technology-related elements		
4.1.1 Condition	Targeted condition	Clinical focus points
		Complexity
4.1.2 Value Proposition	Value Proposition	Match with clinical focus points (DVP)*
		Fit with clinical workflow (DVP)
		Retrievability raw data (DVP)
		Financial injection (UVP)**
4.1.3 Technology	Features	Complementary hardware
		Features according to the wider system
		Validity proof

"DVP"* means downstream value proposition, *"UVP"* means upstream value proposition.

4.1.1 The targeted condition

The interviews pointed out that the desired role and added value of AI are dependent on the targeted condition, especially the belonging clinical focus points and its complexity. The haemato-oncological field contains multiple disease patterns that are generally severe conditions. Luckily, many treatment possibilities have been developed over the past decades. Early diagnosis, accurate disease identification and close monitoring are key[6]. Dependent on the clinical scenario being targeted, different clinical focus points are set. For example, *flow cytometry expert 4* said ***"In our lab, we do routine diagnostics, and the desired benefit of AI would be an increase in workflow. We need faster results so we can handle more samples. AI could take the role of a pathological filter".*** Thus, in high volume routine diagnoses, the emphasis of diagnosis is on speed, to support the currently highly pressured workload. Treatment decisions need to be made as soon as possible to have the best outlook for the patient[7]. As another example, in an MRD setting, the emphasis is rather on accuracy[8]. *Flow cytometry expert 2* said, ***"Objective algorithms that can accurately measure MRD are definitely welcome".*** These two perspectives show that the clinical focus points can vary and should be clarified.

Furthermore, it was found that the complexity of the disease pattern inversely influences the trust of experts in AI. The interviews showed that the more complex the disease pattern, the lower the trust towards the possibility of AI. For example, *flow cytometry expert 1* highlighted that MRD would be a complex pattern to make an entrance: ***"To start with cases such as MRD, I would applaud if AI would succeed in that. Please realize it is a very difficult task. One should start with a very simple disease pattern, for which an algorithm is probably much over-qualified, but people will be accepting. If you start there and show how the software works for those simple cases, you can move into more complicated settings".*** Although facing difficulties for acceptance, expert interviews also emphasized that AI has the potential to assess the most complex disease patterns. However, the clinical expert needs to know what question to ask the data for the algorithm to work correctly. The latter is seen as a difficulty, also showing concerns for AI application for the wider medical field[9]. Therefore, starting with AI for simple disease patterns seems most promising.

Concluding, a clear identification and understanding of the targeted condition is important. Each targeted condition has specific clinical focus points (e.g., accuracy, speed of diagnosis). Identifying these is crucial to define the role and added value of AI. In the haemato-oncological field, the role of AI can thus vary per the targeted condition. Furthermore, the complexity of the disease patterns seems to negatively influence the acceptance shown towards the AI technology. Scepticism was shown for the complex disease patterns, while more optimism was shown for the simple patterns.

[6] Supported by FE1, CE2, IA1, IA2.
[7] Supported by FE1, FE2, FE4.
[8] Supported by FE1, FE2, FE4.
[9] Supported by expert event 7 and 10.

4.1.2 The value proposition

Following the previous section, the desired added value of AI is dependent on the targeted condition, more in specific its clinical focus point. During the interviews, two main desired values came forward: increased accuracy and increased speed, representing the downstream value proposition. Additionally, a desired characteristic of AI mentioned by various interviewees was an easy-to-use and easy-to-implement algorithm[10]. To do so, the innovating actor should clearly understand the clinical workflow and the user requirements[11].

"To define the role of AI, one needs to clearly understand the clinical workflow and functions of users. A seamless integration into the established clinical workflow is a key facilitator for success." – *Innovating agent 3*

Related to that, *interviewee 2* pointed out that a key characteristic of an algorithm should be that the findings are presented as one very clear result, but the user should always be able to retrieve the raw data and go back to the conventional method of analysis. This was said to be especially important when dealing with complex disease patterns; in some cases, the conclusion is easy, but in other cases, the expression patterns can look divergent. Identifying these patterns is still a very experience-based job. Therefore, it is important to have the option to go back to the raw data[12].

Regarding the upstream value proposition, there needs to be a financial incentive. In the case of software, initial development costs can be high as the product needs to be specified and the algorithm needs to be trained. However, after development, the product can be easily scaled. The main barrier in the upstream value proposition for innovating agents is therefore realizing funding[13]. AI based techniques are emerging and still need to prove themselves. Therefore, big validating studies are needed. Sufficient investments are needed to assure the algorithm does not fall short if any setbacks, for example if a trial would be tested the wrong way and would need additional proof. The *wider system stakeholder 2* supported this and stated that ***"an idea does not become big without a major monetary injection".***

Concluding, the value proposition forms an important element of invention in the field. A common ground should be sought between the downstream and upstream value propositions of the algorithm. For the downstream value proposition, the fit with the clinical focus point, workflow and the retrievability of raw data were identified as key points. On the upstream side, financial investments are needed.

[10] Supported by FE1, FE2, FE3, WSS5, IA3, CE4.
[11] Supported by IA3.
[12] Supported by CE1, FE1, CE2, CE3, IA1, IA3.
[13] Supported by WSS2, WSS3, WSS5, IA3.

4.1.3 Technological features

Regarding technological features and capabilities, a lot is possible[14]. However, the technological features the AI solution should offer, are dependent on developments on the interacting hardware side. For example, devices can be restricted to a level of accuracy: certain flow cytometry devices are limited to measure 10.000 cells and use 5 cellular markers only. Whilst AI has already entered the field of single-cell analytics[15], in this case, an AI solution will not drastically increase the accuracy; the hardware limits the features the AI solution can offer[16]. On the other hand, complementary hardware advancements can also drive the need for AI solutions. The high prevalence and severity of blood cancers drives continuous technological advancements[17]. The newest devices measure up to 1.000.000 cells at once and the complexity of the marker panels has evolved to more than 20. The technology is now at a point where divergent markers can be noticed in a very early stage already[18]. These more precise measurements also lead to an increase in provided data. However, on the analysis side, little progress has been made. While the amount of provided data rapidly increases, the speed of interpretation slows down. In fact, the chances of missing important information even increase[19]. The dearth of well-trained and skilled professionals is limiting the growth of this market. Experts do not want to be overloaded with data; they only want relevant data[20]. An incorporation of AI platforms in the workflows and systems is desired, the hardware advancements in this case guided the need for AI[21].

"Over the past decades, flow cytometry hardware started to evolve. More lasers were added, and detecting 5, 20 and now even 50 channels in parallel. The complexity of the panels has evolved. However, on the analysis side, we are still doing the same thing we did 20 years ago, where people are looking at 2-dimensional dot plots. Hence, hundreds of them"- *Wider system stakeholder 5*

AI can come in different formats and features. For example, an algorithm can be generally applicable or tailor-made. An algorithm can enable more precise decision making or fully automated decision making. These options are dependent on many factors of the wider field and should be carefully thought through. Independent of the format and features of the AI technology, any algorithm should extensively have proven its validity to be considered for use in a clinical setting. Interviewees pointed out that legitimacy is mostly related to the technological performance of an algorithm[22]. Preferably, the quality control should even be within the program.

Concluding, the features that AI should offer depends on the complementary hardware. Advancements can restrict possibilities of the added value of AI technologies, but also create a need for algorithm incorporation. Furthermore, the format of the innovation is dependent on the wider system. There is consensus in the field that validity proof is key.

[14] This statement was supported in expert events 2,3,6,7,9 and 10.
[15] Supported by WSS5.
[16] Supported by CE4, FE2, IA2, IA3.
[17] Supported by IA3.
[18] Supported by FE2, IA1, FE4, WSS4.
[19] Supported by WSS2, FE4, IA3.
[20] This statement was supported by expert event 6,7,9 and 10.
[21] Supported by WSS3, WSS5, IA3.
[22] Supported by CE1, FE2, CE2, WSS1, WSS2, WSS3, IA1, FE4, WSS4, CE4.

4.2 Field-level characteristics

When a technology fulfils the technological prerequisites, still not all inventions become an innovation. Although the potential of AI was emphasized, its crystallisation has certainly not been figured out yet[23]. In the aim of exploring whether IE could be an effective strategy, the field-level characteristics – heterogeneity of institutions and degree of institutionalization - were explored. They are presented at three domains: the adopter system (4.2.1), the organization (4.2.2) and the wider system (4.2.3). Findings are used to determine whether the field-level characteristics propose enabling conditions for the phenomenon to occur. An overview of the key findings is presented in *table 5*.

Before the in-depth description of the three levels, some relevant and general field trends are presented. The iterative expert discussions during data collection pointed out that the key findings should all be handled in parallel; treating them as sequential elements during product development could endanger the speed to market. This includes both the technology-related elements as institutional elements. Furthermore, as an overall trend, we saw that the attitude is shifting from non-accepting towards more accepting. It is generally understood that the field is shifting towards more precise measurements, the bigger amounts of data can only add value if we can filter out the relevant findings. AI could be an enabler in this[24]. The use of AI can lead to faster, better, and more cost-effective methods. There is a shift towards consensus on *a* role for AI, although the exact role and format of AI are yet to be defined. Moreover, some other AI technologies with similar purposes as the one of FlowView Diagnostics have been developed. Although none has gained a significant amount of the market share, this does indicate the need for software in the field[25].

"We see that many groups start developing their own solutions. I think that wherever people feel that what they are doing now and what they have always done is not good enough anymore or is not giving the results they want, they are open for new solutions and will be more accepting for innovation." *– Wider system stakeholder 5*

Table 5*: Summary of findings of the field-level characteristics.*

Field-level characteristics			
Domain	**Key finding**	**Heterogeneity / homogeneity**	**Degree of institutionalization**
Adopter system	Attitudes	Heterogeneous	Low
Organization	ICT systems	Heterogeneous	High
	Clinical workflow	Heterogeneous	High
	Type	Heterogeneous	High
	Structure	Heterogeneous	High
Wider system	Policy making	Heterogeneous	High
	Regulatory system	Heterogeneous	Low

[23] Supported by WSS5.
[24] Supported by FE1, WSS1, WSS2, FE3, WSS3, WSS4, FE5, IA3.
[25] An extensive description of other algorithms lays outside the scope of this thesis. However, an in-depth overview of the current availabilities is provided by Cheung et al. (2021). Benefits and limitations could be used indicators for future successes.

4.2.1 The adopter system

On the individual level, heterogeneity of institutions came forward. A variety of attitudes, concerns, and opinions towards AI were mentioned. Although an explicit fear of individuals to be replaced by AI technologies was not expressed by the clinical experts, sceptics did emphasize the risks of AI, which the system cannot take. The negative attitudes were supported by arguments such as a lack of transparency and understanding of how an algorithm works, followed by uncertainty of the risks the algorithm can bring along. Moreover, unclarity on how roles would change was mentioned, followed by a reluctance to change jobs. Clinical experts take pride in their jobs. In their opinion, the experience and expertise of the clinical expert are highly valued and outweighs the potential of AI[26].

"***The common sense of a doctor can never be replaced by an algorithm***" – *Clinical expert 1*

In contrast, enthusiasts emphasized the promising roles AI could bring to the field. When AI can support the clinical expert as a pathology filter, it can take away a part of the workload[27]. The conventional method of data analysis – manual interpretation by the expert – is restricted to the human's capacity and availability. An AI driven pathology filter could be running 24/7, facilitating more expert time dedicated to complex cases. Consequently, this would make the job of the clinical expert even more interesting. Also, it was found that the field should be open-minded for everything that makes the workflow go faster and makes it less prone to human mistakes[28]. As a counterargument to the clinical expertise outweighing the potential of AI, especially for complex cases, *flow cytometry expert 5* indicated that its expertise was trained by seeing many patterns in the past. He stated that if he can be trained, an algorithm can be trained too. It is a matter of having seen and interpreted sufficient complex cases. In general, enthusiasts see AI as a technology that can allow them to be better at their jobs. Organizations that refuse to be involved in the digital transformation, are expected to lag behind[29].

"The fact that we are training experts with pattern recognition experience, means we can train an algorithm to do this as well. Only an algorithm will do it way faster and is less prone to mistakes." *- Flow cytometry expert 4*

Concluding, there is heterogeneity in the field-level characteristics of the adopter system. Individual attitudes towards AI technologies vary between clinical experts. Some are sceptical, others are enthusiastic. Furthermore, the negative arguments given do not seem deeply engrained, but rather seem a consequence of unfamiliarity and understanding. It can be assumed that agency could lead to a change of attitude, therefore, the degree of institutionalization is low. To act as an institutional entrepreneur, one should consider the heterogeneity of attitudes in the field and the corresponding argument, to be able to carefully account for it and push the boundaries of acceptance where necessary. Speakers at the expert event recognized these heterogeneous attitudes and additionally emphasized that sufficient validity proof is key for changing attitudes[30].

4.2.2 The organization

The adopters of clinical AI for haemato-oncological diseases are embedded in organizations, in this case referring hospitals or laboratories. This section studies the field-level characteristics with a specific focus on the hospitals' or laboratories' capacity and readiness to uptake technologies. During the interviews, two elements within, and two elements surrounding the organizations were emphasized of which the field-level characteristics might influence the readiness to innovate. Within organizations, the ICT infrastructure and the clinical workflow are key. Surrounding the organizations, the structure in which it is embedded, and the type of organization came forward.

[26] This was supported by expert event 4, also to be a problem beyond the haemato-oncology subfield.
[27] Supported by FE4.
[28] Supported by FE1.
[29] Supported by WSS1.
[30] This was supported by expert events 3 and 4.

Firstly, the ICT infrastructure was widely described as unstructured, being a key finding related to the capacity and readiness to innovate at the organizational level. Every hospital, department and/or lab uses different programs, that all speak a different language. Moreover, whenever organizations do use similar programs, information can often be stored in different places and different ways in the same system. Moreover, every organization has established its routines, which is hard to change. The ICT infrastructure is heterogeneous and shows high degrees of institutionalization. This is seen as one of the biggest barriers to digital transformation.

"It is such a mess. Everywhere. It makes it impossible to work with. […] And then connectivity is another challenge.* At this point, systems are just unable to communicate with each other*" *– Wider system stakeholder 1*

Secondly, the clinical workflows were found to be heterogeneous, each showing high degrees of institutionalization. Most workflows for severe disease patterns in the field depend on human expertise and are labour-intensive. Every hospital tends to tweak the routines in a way that is most valuable for their expertise. Consequently, departments all have their own routines and ways of doing things, accompanied by feelings of prestige in this expert-based field. These elements lead to a reluctance to change.

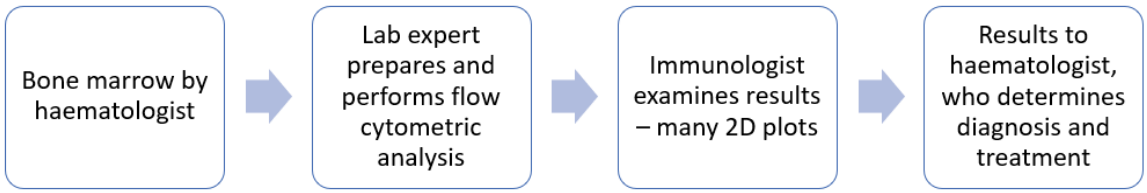
"In Europe, by tradition, every hospital has its own method and micro combination and approach. If you learn a method from your superior, that is what you do. There is a lot of tradition and high reluctancy to change the highly standardized solutions" *– Wider system stakeholder 3*

Moreover, in the specific case of flow cytometry analysis for blood cancers, each workflow leaves space for variation, leading to heterogeneity in quality. The workflow is generally structured as shown in *figure 5* and heterogeneity is a result of the details of each step. First, a bone marrow sample needs to be taken. The quality can vary based on the experience and precision of the haematologist, potentially leading to an under- or overrepresentation of aberrant cells. Thereafter, the sample is prepared for analysis by lab technicians. This means samples are being pipetted and stained with the representative markers for the suspected disease pattern. In most hospitals and labs, this still happens manually, and heterogeneity is dependent on the capabilities of the lab technicians. Furthermore, there is no hard standardization for markers. Selection is based on guidelines, indicating which markers can be an indication for which types of cells, and which cells can be indicators of which pathology. There are various guidelines, such as the World Health Organization (WHO)-guideline. Consequently, all labs have their own assays corresponding to one of the guidelines and tweaked to their own focus. The variety in both the quality and panel selection causes highly unstandardized data in the system. Interviewees acknowledge this lack of standardization, thus heterogeneity, as a barrier for innovation. In fact, some degree of standardisation is needed for AI to work and be trusted, because an algorithm can only be as good as the data being put into it. As *flow cytometry expert 4* stated, ***"garbage in is garbage out"***. This was recognized to be a problem for the wider field, beyond haemato-oncological, as well[31]. As a next step in the workflow, the flow data is being examined by an immunologist. The interpretation process is experience-based and highly subjective. The way certain steps in interpretation are taken, such as gating[32], influences the outcome[33]. Current steps such as cross-validation of results are taken to account for this heterogeneity, to avoid big mistakes. However, according to the *clinical expert 3*, ***"the subjectivity of interpretation is causing most discussion in our bi-weekly interdisciplinary consultations, in which we discuss all cases".*** Lastly, the way results are presented to the clinical expert vary per organization. In academic hospitals, the results are mostly presented as a percentage. In non-academic hospitals, results are generally presented with more context. For most cases, this provided context covers the questions a clinical expert can have.

"In the workflow, there is limited consensus. Small groups might form can align on a consensus panel for a particular application, but we are very, very far away from standardization." *– Wider system stakeholder 5*

[31] Expert event 7.
[32] For those unfamiliar with gating, the interpretation steps are described in *Appendix 2*.
[33] Supported by FE5, WSS5.

Figure 5: *Simplified workflow for diagnosis of multiple myeloma using flow cytometry.*



Thus, the clinical workflow is highly heterogeneous. As many steps in the process are experience-based, it is paired with high levels of pride and often a reluctance to change. The degree of institutionalization is high. A key hurdle for innovation is the costs of implementation, not just monetary, but the implementation of a new solution. It takes time and effort to get used to new technologies. People need to be willing to invest time in learning how to use the algorithm in their workflow. An exact fit of the technology into the specific clinical workflow is desired, minimalizing the implementation costs. Thus, although high levels of heterogeneity of workflow, a thorough understanding is crucial to define how to innovate within them[34].

"To define the role of AI, one needs to clearly understand the clinical workflow and functions of users. A seamless integration into the established clinical workflow is a key facilitator for success." *– Innovating agent 3*

Thirdly, the split in types of organizations was found to be influential for the ease of adoption decision and the value expectation of AI technologies. The organizations can be split into two main subsystems: academic hospitals and non-academic hospitals. They have individual structures and focus points, influencing the perspective and potential seen for AI. Generally, *the non-academic hospitals* analyse and diagnose great volumes of patient samples. The focus is on speed. With the volume of care increasing, hospitals are under large pressure by the government and insurance companies to keep the costs down[35]. These financial pressures lead to criticism towards unknown technologies, especially when the direct benefit is not within the hospital. Therefore, the budget for specialists is strictly capped. In non-academic hospitals, a return on investment within a year should be seen to adopt a technology. This causes the attitude towards innovation to be mostly a wait-and-see attitude unless the business case is extremely convincing[36]. On the other hand, non-academic hospitals were found to have a flat structure, where one enthusiastic clinical expert can be highly influential for the adoption decision process[37]. In contrast, in *academic hospitals,* this was said to be more difficult, as there is a more hierarchical structure passing through several experts and the head of the department, before making an adoption decision. Furthermore, academic hospitals generally deal with lower volumes but more complex cases of a disease. Flow cytometry is for example mainly used for deciphering the cells of patterns in academic hospitals, with the focus on accuracy. Academic hospitals generally have larger budgets, also having a more research-driven and "eager to innovate" attitude. They are looking for an increase in quality[38].

"If an academic hospital can make a better diagnosis, it doesn't matter how much it costs. Of course, it does not have to be thousands of euros per run. But you understand what I mean" *– Wider system stakeholder 2*

Lastly, the structure in which an organization is embedded, emphasizing the costs and payment structure of the health system, came forward as a field-level element of which the characteristics might influence the innovative possibilities, being influential for the capacity and readiness to innovate, and the ease of adoption decisions. The Dutch health care system consists of insurance companies, accredited quality companies, medical specialist working groups, inter-hospital collaborative initiatives and several governmental organizations, all influential on the uptake of innovation. The

[34] Supported by WSS5 and expert event 9 as a requirement for the wider field.
[35] Supported by WSS1, CE3, and cross verified with additional expert conversations.
[36] Supported by WSS1.
[37] Supported by CE3.
[38] Supported by FE1, FE2, O2.

organization, mostly being the hospital, and the paying organization, for example being the insurance company, are central. Complexity is caused by the fact that often the costs are for the hospital, but the gains lay outside of the hospital. For example, an innovation that leads to fewer people visiting the hospital also leads to discussions on reimbursement with the health insurance companies, which was named as a hassle and key barrier[39]. Moreover, agreements between hospitals and insurance companies can be negotiated per hospital, per application, and might vary widely[40]. This heterogeneity of settings also reflects in varying attitudes toward the technology and potential changes induced by it[41]. Although hospitals are free to set up their own agreements, once agreements are made, they tend to stick to agreements they have. The field is quite conservative to change. Thus, the structure in which organizations are embedded is heterogeneous, showing a high degree of institutionalization.

Concluding, field-level characteristics of the organization domain are heterogeneous and show high degrees of institutionalization. Key findings which should specifically be considered were the field-level characteristics of the ICT systems, the clinical workflows, the type of organizations and the structure directly surrounding the organization. These were found to be influential for the capacity and readiness to innovate, and the ease of adoption decisions.

4.2.3 The wider system

Organizations also are connected and influenced by more distant stakeholders and structures. Considering this wider system, organizations are connected to specialism-specific co-working groups, working on, and exchanging the newest developments and focus areas. Also, there are inter-organizational collaborative programs with shared roadmaps and focus points. However, in the end, all hospitals were said to be bounded to their organization-specific infrastructure, expertise, roadmaps, and priorities[42]. The organizational heterogeneity was found to currently hamper innovative activities as a wider system. The failure of the field is being recognized and responded to by governmental initiatives, starting with incentive programs and subsidy programs (e.g. VIPP[43], MEDMIJ[44]) to harmonize the field[45].

"It takes at least two to collaborate. And that can be tough. In the end, every organization has its own roadmap for development and innovation and will always depart from its own point of view and architecture. If investments need to be made to collaborate in other systems, while you already have something similar, it simply will not happen. There is a lack of shared goals in the field" *– wider system stakeholder 1*

Furthermore, as part of the wider health system, the regulatory system was emphasized. The legislative system in the field is defined on a European level. This law is broad and sets expectations to which all medical devices of all Member States should comply. Therefore, the law is homogeneous. Moreover, the degree of institutionalization is high; without complying with the law, a product is not allowed on the market. This was also found to be the general perception of the regulatory system, very strict and homogeneous, often referred to during the interviews as one of the biggest barriers for innovation in the field[46]. However, it was also found that in order to comply with the law, a wide variety of standards and norms are developed specific per country, per sector, per product. Therefore, the regulatory system is in practice organized in a quite heterogeneous way and offers opportunities for actors to smartly move within the requirements of the field. The heterogeneity thus in fact offers opportunities for change.

"Actors often place a technology into a harness that prevents it from moving, blaming legislation for this. However, the legislative system offers lots of freedom to move. The law is a broad expectation that a product shall be safe and

[39] Supported by WSS1.
[40] Supported by IA1.
[41] Supported by FE5.
[42] Supported by WSS1, CE3.
[43] The VIPP program is an acceleration program for information exchange in the medical sector. More information can be found on https://www.vipp-programma.nl/.
[44] The MEDMIJ program supports secure and reliable data exchange in the health sector. More information can be found on https://www.medmij.nl/en/.
[45] Supported by WSS1.
[46] Supported by WSS5.

effective; the requirements that should be fulfilled. How it is fulfilled, is a large puzzle of all possible standards and norms that should be carefully chosen and used" – *Innovating agent 4*

More in specific, the regulatory pathway for clinical AI was described. Clinical AI innovations are generally classified under the regulatory system of medical devices, being all products or equipment intended generally for medical use (EMA, 2021). All medical devices need to comply with the same law, to maintain a health system with reliable products only[47]. Depending on the role of the device, the key laws medical devices should comply with are the Regulation (2017/745) of Medical Devices (MDR) (2017/745) and/or In-Vitro Diagnostic Devices (IVDR) (2017/746). This regulatory system is developed for all European Member States and is led by the European Medicines Agency (EMA). Thus, what is expected from a device to be legally on the market, are strict requirements. However, how to comply with the law, is organized in a more heterogeneous way[48]. A wide spectrum of norms and standards were developed both on a global level (ISO-standards), European level (IEC-standards) and national level (for The Netherlands, NEN-norms). Additional elements might be added, for example, in the case of clinical AI, specific standards for privacy protection and security play a key role to comply with the legislative requirements. The required documentation is depending on the functionality and risk. A low-risk device (also known as *class I*) can get certified when having a quality system in place, a medium-risk device (also known as *class IIa or IIb*) and high-risk devices (also known as *class III*) should go through validation processes on quality and safety providing data and technical documentation, as well as post-market surveillance processes. For example, AI technologies intended as clinical decision support, which was mostly focussed on in the interviews, would be classified as class IIa[49]. Accredited notified bodies are normally used to conduct conformity assessments. When complying with the law, medical devices can acquire a CE-mark[50].

Concluding, the wider system shows lots of heterogeneity in terms of priorities and aims. Initiatives to harmonize the field are being started through policy making, but this currently happens in a heterogeneous way. Furthermore, the regulatory system was pointed out as a key domain in the wider system. The institutional environment is organized in a homogeneous way on a European level, whilst it is heterogeneous on a national level. The degree of standardization is high.

[47] Supported by IA4.
[48] Supported by IA4.
[49] According to ANNEX VIII, 6.3 Rule 11 of MRD: *"Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause: death or an irreversible deterioration of a person's state of health, in which case it is in class III; or a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb. Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb."* (European Parliament and the Council of the European Union, 2017).
[50] This is an abbreviation for Conformité Européenne, being a prove of safety and performance of the device (European Medicines Agency, 2021).

4.3 Actor's social position

In addition to the field-level characteristics, the actor's social position is said to be a potential enabling condition for IE. It can influence the likeliness of an actor to act as an institutional entrepreneur. The optimal position was said to vary per case. In the scope of this thesis, importance was emphasized to connect to central actors. Both at adopter as organization level, a main element pointed out during the interviews was to connect with a key opinion leader when innovating in the field[51]. Key opinion leaders are central players in their respective disciplines and their opinion is highly valued by peers. Ideally, a key opinion leader is an enthusiast that wants to fight for a new technology. These are central players such as clinical experts or lab experts, depending on the roles per organization and workflow, and the targeted role of the AI technology. In the specific case of FlowView Diagnostics, a key opinion leader would be someone involved in the flow cytometry unit and working on the intersection with haematologists. Prominent channels through which ideas are mostly being picked up are through congresses, working groups and/or scientific literature. Furthermore, a conservativeness to change of organizations, and the wider system it is embedded in, was pointed out. Tight connections are often established with the big manufacturing companies delivering hardware, which often also have legal agreements through contracts. To enable change, a strategic social position would include connecting to those central players.

Furthermore, multiple embeddedness in the data sciences field and the haemato-oncological field was found to be key. The interviews indicated that unfamiliarity with how algorithms work, lead to fear[52]. For an algorithm to be accepted, the clinical expert should have a better understanding of how algorithms work, while the data scientists should have a better understanding of what data it is dealing with. A high level of variation in data and standards is not necessarily a bad thing. The unawareness of variations is very dangerous; only when knowing how an algorithm was trained, one can anticipate the mistakes it can make [53]. Therefore, when developing an AI innovation, multiple embeddedness of the innovating actor – being an individual or a set of multiple individuals - is key to form a bridge between data science and the medical field. The baseline understanding in all involved disciplines should be improved. In addition, speakers at expert events supported these findings to be relevant for the wider context of AI in the medical field. It was argued that in general in the field, deep learning (a subset of AI) is not the same as deep understanding, emphasizing that algorithmic developments should go hand in hand with a deep clinical understanding [54].

"For AI to work, we need someone who translates between the data scientist and the clinical specialist. Because a big problem is that a data scientist often has less feeling with what exactly is being measured and why, and a specialist needs to know if the algorithm was trained right. And those two need to interact to come to a well-working algorithm." ***–*** *Wider system stakeholder 2*

Furthermore, it was emphasized that the social position is especially important as clinical AI in haemato-oncological is still emerging. By connecting to key opinion leaders, bigger central players in the field and through multiple embeddedness in both the data sciences field as the medical field, the innovating actor can stay aware of the latest developments in the field. For example, in an emerging field, regulations can be in development, or other institutional elements might be changing. By positioning strategically, the innovating actors can assure to act appropriately to changes in the field, thus, staying resilient.

Concluding, the actor´s social position is said to be important for the attitudes towards a technology. Ideally, the innovating actors should be connected to key opinion leaders in the field, central players of the wider system (such as manufacturers) and be embedded in both the data sciences field as the medical field. By doing so, barriers can be minimalized.

[51] Supported by CE2, WSS1, WSS2, CE3, FE5, WSS5, IA3.
[52] Supported by WSS1.
[53] Supported by FE5, IA2 and supported by expert event 7.
[54] Expert event 9.

5. Analysis

Following the extensive description of the findings chapter 4, this chapter analysed the key findings in the context of the integrated theoretical framework and analysed the dynamics between them. Following the abductive research approach, theoretical suggestions were made.

The theoretical framework indicated three technological-related elements to be considered when innovating with complex technologies in the medical field: the condition, the value proposition, and the technology. Analysing the findings, the three elements are closely interwoven, and key findings should be carefully considered when innovating in the field. Specifying the targeted condition is key to identify and establish *a fit with the clinical focus points*. This can vary per disease. As limited AI success cases are established in the field to date, *starting with a simple disease pattern* seems most appropriate to create familiarity. Furthermore, retrievability of the raw data was emphasized as part of the desired upstream value proposition and is therefore a crucial feature of each technology. Thus, to be considered as legitimate, sufficient *validity proof* is key. This is however directly related to the complexity of a disease pattern, as more complexity might require more validity proof. To establish all technological elements, *a financial injection* is needed to enable technological developments and validity proof activities. These technological prerequisites should be fulfilled to create a favourable environment for IE to occur. The technology-related elements of the integrated framework can thus be specified into *fit with clinical focus points, simple disease pattern, validity proof and financial injection*, representing the technology-related enabling conditions for IE to occur.

Furthermore, the field-level characteristics were examined and analysed at three domains: the adopter system, the organization, and the wider system. From a theoretical perspective, institutional heterogeneity and low degrees of institutionalization are expected to be enabling IE. *The adopter system* was found to have heterogeneous institutions and a low degree of institutionalization. The heterogeneous perceptions on the adopter level were found to not be set in stone and provide opportunities to be changed. In line with theoretical expectations, the adopter system is expected to provide an enabling condition for IE. *The organizational level* showed high levels of heterogeneity and high degrees of institutionalization. In fact, the findings indicated extreme levels of heterogeneity, emphasizing the need for standardization before (institutional) change can happen. The findings suggested that there is an optimum level of heterogeneity in institutions. For organizations in the haemato-oncological field, this optimum is currently surpassed and a shift towards more standardization is needed to become enabling for IE. The heterogeneity was found to most disturbing concerning ICT systems, clinical workflows, the type of organizations and the structure in which the organizations are embedded. In addition, the high degree of institutionalization is not enabling IE, as pride and tradition within and surrounding organizations are causing reluctance to change. However, recognizing the innovation barriers of organizations, policy initiatives on a higher level were launched to harmonize the field and break the high degree of institutionalization. This can potentially change field-level characteristics in the future, discussed in subchapter 5.1.

Lastly, we analysed the wider system. A remarkable finding was that the regulatory system was frequently mentioned as a barrier for innovation in the field. Regulatory compliance is a hard requirement for commercialization and use, therefore, the degree of institutionalization in the field is high. Whilst the regulatory system is generally perceived as a homogeneous and strict environment, regulatory experts indicated that the structure in practice provides lots of freedom to move. Although the high degree of institutionalization is not necessarily enabling for IE, the heterogeneity in perceptions in fact provides opportunities for IE to create a new shared understanding of an appropriate regulatory pathway for clinical AI. Additionally, the recently emerging policy activities are not yet standardized or highly institutionalized, thereby offering an enabling environment for IE to occur. Consequently, contradicting the general perception of the wider system hampering innovation in the field, the wider system provides an environment in which institutional entrepreneurs could help to strategically push the system boundaries in favour of the technology. The analysis of field-level characteristics is summarized in *table 6.*

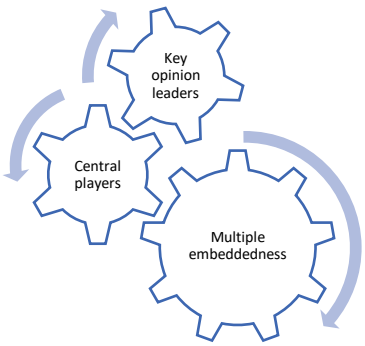
***Table 6**: Field-level characteristics of AI innovation in the haemato-oncological space.*

Field-level characteristics						
Domain	**Key element**	**Heterogeneity / homogeneity**		**Degree of institutionalization**		**Enabling IE?**
		Perceived	**Finding**	**Perceived**	**Finding**	
Adopter system	Attitudes	Heterogeneous	Heterogeneous	Low	Low	+
Organization	ICT systems	Heterogeneous + (*)	Heterogeneous +	High	High	-
	Clinical workflow	Heterogeneous +	Heterogeneous +	High	High	-
	Type	Heterogeneous +	Heterogeneous +	High	High	-
	Structure	Heterogeneous +	Heterogeneous +	High	High	-
Wider system	Regulatory system	Homogeneous	Heterogeneous	High	High	-+
	Policy making	Homogeneous	Heterogeneous	Low	Low	+

** "Heterogeneous +" means extremely high levels of heterogeneity.*

Furthermore, it was theoretically expected that the actor's social position would influence perceptions of a field, perception of legitimacy and their access to resources. It is generally understood that the optimal social position for IE to occur should be defined per specific context. In the scope of this thesis, three requirements came forward. Firstly, the actor should connect to and involve key opinion leaders in the field during the development and innovation process. Key opinion leaders were central players in their respective disciplines and their opinion is highly valued by their peers. Secondly, a connection with key players in the wider field is crucial as it was indicated that organizations often tend to stick to the already established agreements. When connecting to central players such as big flow cytometry manufacturers, reluctance to change might be diminished. Thirdly, the theoretically expected need for embeddedness in multiple fields was confirmed. Embeddedness in both the data sciences field and medical field was highlighted to be important; both fields should be actively involved in the development process towards innovation. Multiple embeddedness can increase familiarity of potential benefits and risks of both sides, and consequently, decrease barriers of trust. The actor's social position can create legitimacy to some extent, in terms of creating familiarity and understanding how both fields work. In terms of access to resources, the social position can mainly enable access to human resources and knowledge of the fields. Lastly, the actor's social position was found to be a facilitator for resilience, as it enables access to information of the entire field, being aware of the latest (expected) developments and changes. Key elements of creating a favourable actor's social position are visualized in *figure 6.*

***Figure 6:** Key elements of adopting an enabling social position for IE.*



Connecting the analysed concepts, the following interlinkages were found. To fulfil the technology-related elements, a strategic social position is key. Being connected to and involving both fields and key opinion leaders, an iterative development process could facilitate a good fit into the system, create familiarity and awareness of potential risks and

benefits, share early success stories, and allow for awareness of (future) hardware developments. These elements can also facilitate IE activities at the adopter system level, as adopters' concerns might be taken into account. Multiple embeddedness and connecting to key opinion leaders thus facilitate a thorough understanding of and fit with the clinical workflow. Furthermore, establishing a central position in the field and connecting to central players such as big manufacturers, could alleviate reluctance to change. In the case of tighter connections or even collaborations with those central players, one could expect this to provide access to bigger financial injections. Furthermore, validity proof was pointed out as a key requirement for legitimacy. Enabling a favourable social position can facilitate access to needed databases, and the spread of success stories when proven valid. Thus, the technology-related elements are closely related to the actor's social position. These activities can also reinforce or change institutions of the adopter system.

Concerning the field-level characteristics, the biggest hurdles for both technological as well as institutional change were identified for organizations. The extremely high levels of heterogeneity make it unlikely for IE to occur. Until there is some form of standardization, the development of field-wide algorithmic innovations will remain a challenge. To circumvent this problem, as a first step, institutional entrepreneurs could act within organizations. The actor's social position is key to understand the institutional and technological environment per organization and to strategically act upon it. Regarding the high degrees of institutionalization in organizations, wider system policy initiatives are providing pressure and (financial) incentives for this to change. Consequently, the actor's social position is also relevant to stay aware of developments in the wider field. If for example policy initiatives would lead to increased standardization on an organizational level, the possibilities of IE could be expanded.

Concluding, although a lot is possible technologically, the crystallization and system fit remains a challenge. This chapter analysed the current requirements, challenges, and opportunities of the technological and institutional environment for AI development in the field. Additionally, it was emphasized that the key findings should all be handled as complementary elements instead of sequential elements, to avoid endangering the speed to market. It was found that the technological and institutional environment can partly be enabling for IE, with the institutional environment of the organizations offering the biggest challenges. Building on the findings of this analysis, although not included in the findings chapter, the next subchapter additionally presents remarkable findings on the future outlook of the field, as this was considered relevant for potential IE opportunities in the future.

5.1 Future outlook

The analysis above is presenting the current situation. However, the field is emerging, and changes are expected. During the interviews, two expected changes were mentioned that could potentially affect the possibilities of IE in the field.

- Per May 2021, with a transitional period until May 2022, a new regulation is expected, namely the In Vitro Diagnostics Medical Devices Regulation (IVDR). The main aim of this regulation is to further standardize the field. This new regulation for example prohibits the use and development of personalized assays by individual labs whenever there is a CE-marked assay available for that specific purpose[55].
- On the complementary hardware side, advancements are also made. Hospitals are increasingly adopting the newest technologies, such as the ACQUIOS flow cytometer of Beckman Coulter, for example allowing for automatic pipetting which reduces variation in the sample preparation[56].

These future expectations are promising for AI developments, as these limit the heterogeneity at an organizational level, bringing the field closer to an optimum for IE to be enabled. This can be expected to positively impact IE opportunities in the field. The actor's social position was emphasized to be crucial to stay resilient to act upon the future changes.

[55] Supported by IA1, IA4.
[56] Supported by IA1, WSS5.

6. Conclusion

Over the recent years, the medical field has been flooded with data. However, the field has been facing a "data rich, information poor" problem: the high volumes of data are exceeding the human capacity of analysing it. This is especially true for the haemato-oncological field: the high prevalence and severity of blood cancer has led to major technological advancements, providing lots of data. However, the scarcity of well-trained and skilled professionals is restraining the efficient use of this data. As AI algorithms can be trained to accurately recognize these patterns or deviations within seconds, they could consequently prove to be the next step in improving patient survival rates. Although significant academic attention is given to the development of AI technologies, real-world deployment lags behind. This problem was referred to as the invention-innovation gap, invention referring to an idea, and innovation referring to the commercialization of that idea. A need for further research on this topic was expressed, leading to the empirical aim of this thesis; to better understand and contextualize the invention-innovation gap, specifically for AI developments in the haemato-oncological field.

To analyse this problem, the starting point of this thesis has been the idea that innovation does not happen in isolation but is rather part of a wider system. In that perspective, this thesis took an institutional approach to study the problem. Institutions referred to the habits, routines, and shared concepts in the field, as well as norms and regulations. An institutional entrepreneur referred to actors who actively create new, or transform existing, institutions to create an environment in which technological change can thrive. To make this perspective more applicable for complex technologies in the medical field, a technological component was added, and domains to specialize the IE approach were defined based on the NASSS framework by Greenhalgh et al. (2017). An integrated framework was created.

The research problem and theoretical approach has led to the following research question: ***What are the institutional facilitating factors and barriers for AI innovation in the haemato-oncological field, and could institutional entrepreneurship be a suitable strategy to help overcome the invention-innovation gap?*** Guided by the integrated framework, three sub-questions were formulated: *(1) What are the relevant technology-related elements? (2) What are the key field-level characteristics in the haemato-oncological space? (3) How does the actor's social position influence the perception of the field?* A single case study design and abductive approach were used to study the problem and led to the following answers:

SQ1: *What are the relevant technology-related elements?*

The findings of this thesis supported the assumption that technological change and institutional change are complementary to facilitate technological innovation. Key technological considerations were that AI applications in the field should first be developed for a simple disease pattern. Early developments should be shared to increase familiarity and trust within the field. Furthermore, a seamless fit into the clinical workflow should be achieved. This indicates the opportunity for the IE to identify the clinical focus point, routines, and workflows to define the role of AI. When doing so, the hardware possibilities and (expected) advancements should be carefully considered. Furthermore, validity proof is key. No mistakes can be made, and a significant amount of proof is required to create trust. For all development steps along the way, financial injections were found to be key.

SQ2: What are the key field-level characteristics in the haemato-oncological space?

The field-level characteristics were analysed for three domains: the adopter system, organization level and wider system. The adopter system showed heterogeneity and low degrees of institutionalization. Organizations and the wider system showed heterogeneity and high levels of institutionalization. Although enabling conditions for IE would only be expected with heterogeneity of institutions and low degrees of institutionalization, the analysis pointed out opportunities for IE at both the adopter system and the wider system.

In the *adopter system,* the main institutional consideration was the individual attitudes. These vary widely from being enthusiastic – AI should do everything the clinical experts do, only faster and less prone to mistakes -, to seeing little

potential – the common sense of a doctor can never be replaced**.** However, the heterogeneous attitudes showed low degrees of institutionalization, providing opportunities for change. For example, key arguments given by pessimistic views included a lack of familiarity, understanding and trust. An institutional entrepreneur should be highly aware of the heterogeneous attitudes within the field and focus its work to create a new mutual understanding. Consequently, in line with theoretical expectations, the adopter system seems to be a suitable environment for institutional entrepreneurs to thrive. Regarding the *organization,* key considerations were field-level characteristics of ICT systems, clinical workflows, type of organization and the structure in which the organization is embedded. For all four of them, high levels of heterogeneity and high degrees of institutionalization were identified. It was found that the heterogeneity in fact surpassed an optimal level of heterogeneity, presenting a barrier for IE. Standardization of systems, and quality standards of data are needed to train field-wide AI solutions. For the *wider system*, the key considerations were policy making and the regulatory system, both showing heterogeneity in institutions and high degrees of institutionalization. Mainly the regulatory system was identified as a hurdle. However, for the emerging field of clinical AI, regulation and policy making is constantly evolving, showing opportunities for IE. The regulatory system should be seen as a puzzle in which pieces can be strategically chosen, rather than a harness in which actors cannot move. Thus, the wider system presents opportunities for IE to occur.

SQ3: How does the actor's social position influence the perception of the field?

Whilst an actor's social position was theoretically expected to be enabling IE, the optimal social position was not yet defined. In this research, it was highlighted that with regards to AI innovation in the haemato-oncological field, the social position is indeed expected to influence possibilities for innovation. The main considerations were the connections to key opinion leaders, central players in the wider field and multiple embeddedness.

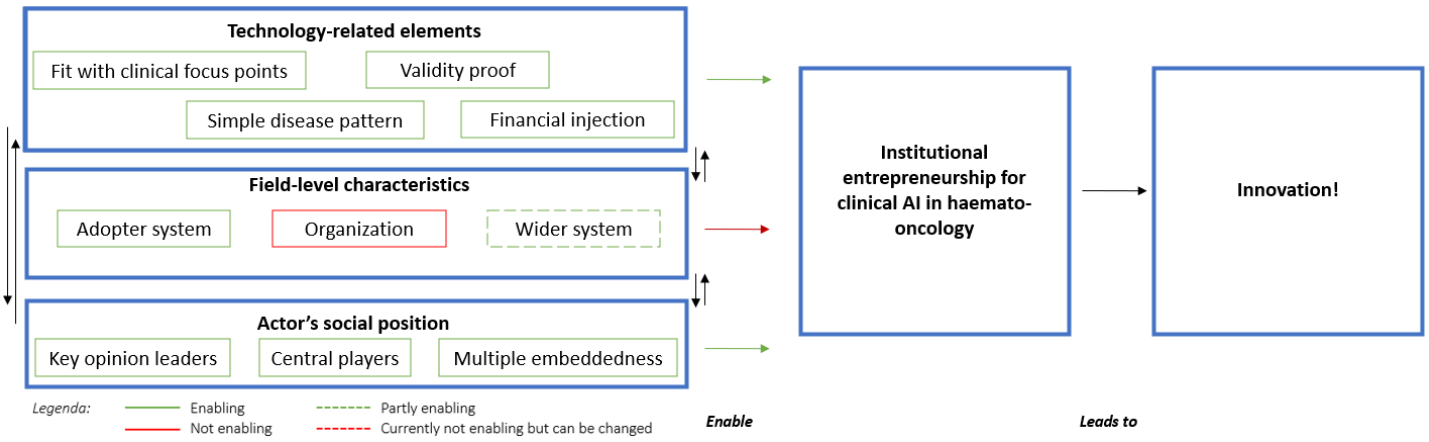
Within the field, connecting to and involving key opinion leaders in the development process is crucial to increase a fit with the provided data, clinical focus points, workflow and to create familiarity. For IE to be possible, this is expected to be most important at the adopter level. At an organizational and wider system level, connecting to central players in the field - such as manufacturers - is crucial to deal with reluctance to change due to fixed contracts, as well as to potentially facilitate larger financial injections. Furthermore, multiple embeddedness of the innovation actors within both the data sciences field and the medical field is needed to facilitate an iterative development process. The data scientist needs to understand what is being measured and why, and the medical specialist needs to understand how an algorithm is being trained. An understanding of AI's basics will need to become part of physicians' statistical literacy, needed for the identification of challenges that may accompany AI technologies. Only then, the potential and risks of the proposed algorithm can be defined.

Concluding the three sub-questions, an answer to the main research question can be formulated.

RQ: What are the institutional facilitating factors and barriers for AI innovation in the haemato-oncological field, and could institutional entrepreneurship be a suitable strategy to help overcome the invention-innovation gap?

The institutional facilitating factors are field-level characteristics at the adopter system level and arguably at the wider system level in the medical field, and the actor's social position. The main institutional barrier is the high heterogeneity at the organizational level within the field, combined with the high degrees of institutionalization. The technological prerequisites – the fit with the clinical workflow, simple disease pattern first, validity proof and a financial injection - should be fulfilled to provide an environment in which IE can help bridge the invention-innovation gap. Concerning the field-level characteristics, IE is likely to occur on the adopter system level and wider system level. On an organizational level, IE is less likely to occur. With regards to the actor´s social position, connecting to key opinion leaders, central players in the field and multiple embeddedness, increases the likeliness of acting as an institutional entrepreneur. All elements mentioned above should be focused on in parallel; the elements are highly interwoven and complementary, and moreover, treating them as sequential elements could limit the speed to market of the innovation. A concluding integrated framework of the opportunities for IE in the haemato-oncological field is presented in *figure 7*.

Figure 7: *Concluding integrated framework for AI in the haemato-oncological field.*



Concluding on whether IE can help overcome this invention-innovation gap, the answer to this question is partially yes. It was pointed out that AI is not the isolated answer to the "data rich, information poor"-problem; in the assumption that technology is part of the solution of the system, a holistic approach was taken exploring possibilities to change the field. The haemato-oncological field does not provide a fully supporting environment for IE to occur. Therefore, IE is currently not expected to help overcome the invention-innovation gap on a field level. Standardization on the organizational level is needed first. To circumvent the organizational barriers, IE can thrive for tailor-made AI inventions for organizations or regions in which organizations show less heterogeneity. This would mean that algorithms are tailor-made for the structures, types of organizations, used systems and clinical workflows. When doing so, there is in fact a role for institutional entrepreneurs to facilitate the institutional change on an adopter system and wider system, in parallel with strategic positioning and guiding the technological developments. Although not easily scalable, tailor-made solutions seem currently most appropriate in the field, and IE is needed to facilitate the step from invention to innovation.

The future outlook indicated that new regulations are announced, and increased standardization on an organizational level is expected. New developments could create momentum for institutional entrepreneurs to move to a wider field-wide focus and to facilitate institutional and technological change in the system. Thus, if developments lead to more standardization on an organizational level, development opportunities for field-wide algorithmic innovations should be reconsidered. For the emerging developments in the haemato-oncological field, it was recognized that the innovating agents' social position is key, enabling the resilience to constantly adapt to a changing environment and strategically use it to push institutional and technological changes, facilitating innovation.

"AI will not replace the clinical expert. The clinical expert who refuses to use AI, will be replaced." **–** *Flow cytometry expert 4*

7. Discussion

This chapter discusses the theoretical and empirical contributions and three limitations - the external validity, the reliability, and the scope – of this thesis. This is followed by future research suggestions. We conclude with a presentation of the management implications for the case studied in this thesis, FlowView Diagnostics.

7.1 Contributions & Limitations

Concerning contributions, this research both contributed theoretically and empirically to the field. It presented an institutional perspective towards the invention-innovation gap for clinical AI within the haemato-oncological field, taking into consideration the technological nature of clinical AI, and the complexity of the medical field. This thesis has proposed and proved a new integrated theoretical approach, offering an institutional perspective to complex technological innovation in the medical field. To date, the applicability of the IE approach to technological innovation has arguably been limited. This research specified the IE approach of Battilana et al. (2009) for domains of the medical field by complementing it with technology-related components retrieved from the NASSS framework of Greenhalgh et al. (2017). Consequently, this new IE approach offered an institutional perspective on the invention-innovation gap in the field. Furthermore, Greenhalgh et al. (2017) have explicitly encouraged the academic community to explore the applicability of their framework for other purposes. In this thesis, the domains of their framework were used to guide research in the medical field, thereby answering their needs.

The empirical contribution of this thesis is the understanding and contextualization of the invention-innovation gap. This thesis offered a new perspective to the problem, that might give direction to strategic action to deliver more innovation in the field. In addition to the research conducted on identifying facilitators and barriers in the field, this research examined possibilities on how to deal with the facilitators and barriers in the field. The practical relevance was stated in the introduction of this research – considering the advancements towards more precise measurements and the challenge of translating the (increasing amounts of) data to information, AI can be the next step in improving patient survival rates. We hope this research can bring the community one step closer to make AI clinically impactful.

Although this research selected the most appropriate design for the intended study, the research design - a qualitative research design, using a single case study - showed three limitations that should carefully be considered. Firstly, limited reliability is a general critique on qualitative research. This type of research is much dependent on the interpretation of the researcher, which is widely concerned as showing a lack of methodological rigour. During this research, anticipating steps have been taken to clarify the epistemological groundings, consequently minimalizing this limitation. For example, an interview guide and a coding scheme were used, where notes of all considerations were made throughout the process. Empirical and theoretical findings were all documented as soon as possible, transcripts of all interviews were made within 48 hours[57] and key findings were iteratively discussed with experts in the field. To avoid repetition, some codes that fitted into multiple variables were not always fully discussed. Although recognized as a reliability-related limitation, we believe the research problem was sufficiently addressed by restricting the presentation of findings to the key findings per category. Furthermore, the Fleiss' kappa was used to decrease the researcher's bias.

Secondly, when using a single case study, the limited external validity of the results - the basis for generalization - is an unavoidable critique. Although providing a rich understanding of the institutional and technological context of the case, findings cannot be assumed to be representable for the entire medical field. Generalizability was addressed as much as possible by selecting interviewees representing the entire haemato-oncological field, thus not only related to the case – FlowView Diagnostics - or flow cytometry. Furthermore, findings from the interviews were iteratively validated with the most recent knowledge presented at expert events. Whenever findings were in line with information provided at expert events considering the wider medical field, this was seen as an indication that the finding of our research was in fact

[57] The transcripts can be obtained on request by contacting the author.

representing a phenomenon that is recognized for the entire field. Although efforts were made to minimalize this limitation, it remains an unavoidable issue in this design.

Thirdly, a topic came forward during the interviews and events that fell outside of the scope of this thesis but might nonetheless be relevant for bridging the invention-innovation gap, namely the intellectual property protection strategies. To date, a key intellectual property protection strategy for medical technology has been patenting, granting exclusive rights to use the invention for a limited period. This structure is designed to incentivise innovation, as the invention-innovation process can be long and expensive, and exclusivity can facilitate returns on investment. Clinical AI technologies should therefore be protected as well. Interviewees and experts at events pointed out that patents do not protect software. Indirect patents can be sought – for example by protecting the method by which the AI functions. Furthermore, algorithms could be protected in the form of trade secrets or copyrights. However, the most preferred consideration concerning clinical AI is the protection of the input data, so others cannot use the data to train similar AI technologies. Data can be protected for example by gathering unique data, by collaborating with a unique partner or by transforming the data in such a way to make it unique, so others cannot copy it. Due to the focus and scope of the research, this topic was not explicitly investigated. Nonetheless, including elements such as intellectual property strategies might offer a relevant alternative perspective to the problem.

7.1.1 Future research suggestions

Based on the discussed contributions and limitation, three future research directions are suggested. Firstly, this thesis presented a first step in the institutional approach to the problem, as it examined *whether* IE could be a suitable strategy to overcome the problem. The analysis indicated that the haemato-oncological field shows opportunities on a local level and is expected to show opportunities for the entire medical field in the future. A next research step would be to identify *how* institutional entrepreneurs should function in the field. Lawrence et al. (2009) theorized upon this, referred to as institutional work, defined as *"the purposive action of individuals and organizations aimed at creating, maintaining and disrupting institutions"* (Lawrence et al., 2009, p. 215). Battilana et al. (2009) reflected on this topic as a subsequent step after evaluating the enabling conditions for IE to occur. To date, institutional work has been widely applied within the academic community for a variety of empirical settings. In line with the design of this thesis, it might need to be adapted for specific application toward technological change in the medical field.

Secondly, building on the external validity limitation of this research, it would be of added theoretical value if the similar integrated framework and coding scheme were applied to different empirical settings, for example to different subfields of the medical field. In addition, it might be interesting to explore the topic in a different nation or even on a European or global level. This could improve the generalizability of the findings and would contribute to a better understanding of AI in the medical field in general.

Thirdly, building on the scope limitation of this thesis, studying equally important but out-of-scope topics such as intellectual property protection strategies are recommended as these might be impactful elements in this emerging field too. Related to that perspective, it might also be valuable to study the same research problem from an alternative theoretical approach to create a more holistic view. A suggestion for such an alternative approach could be the multi-level perspective, studying socio-technical change through the interaction of three levels: the niche, the regime, and the landscape. The niche can be represented by the AI developments, the regime can be the wider system including regulatory system and policy contexts, and the landscape might be the general emergence of information technologies. For example, this theory could be applied to the research finding that showed high restraints for information sharing due to the heterogeneity on an inter-organizational level. The findings pointed out that as a reaction to this problem, policy initiatives such as the VIPP program provide financial incentives to harmonize the field. This could be seen as regime level activity from the multi-level perspective theory, creating momentum for niche developments to emerge. In the aspiration of bridging the invention-innovation gap, future research studying the multi-level perspective dynamics and potential regime openings might be valuable for niche developments to mature.

7.2 Management Implications for FlowView Diagnostics

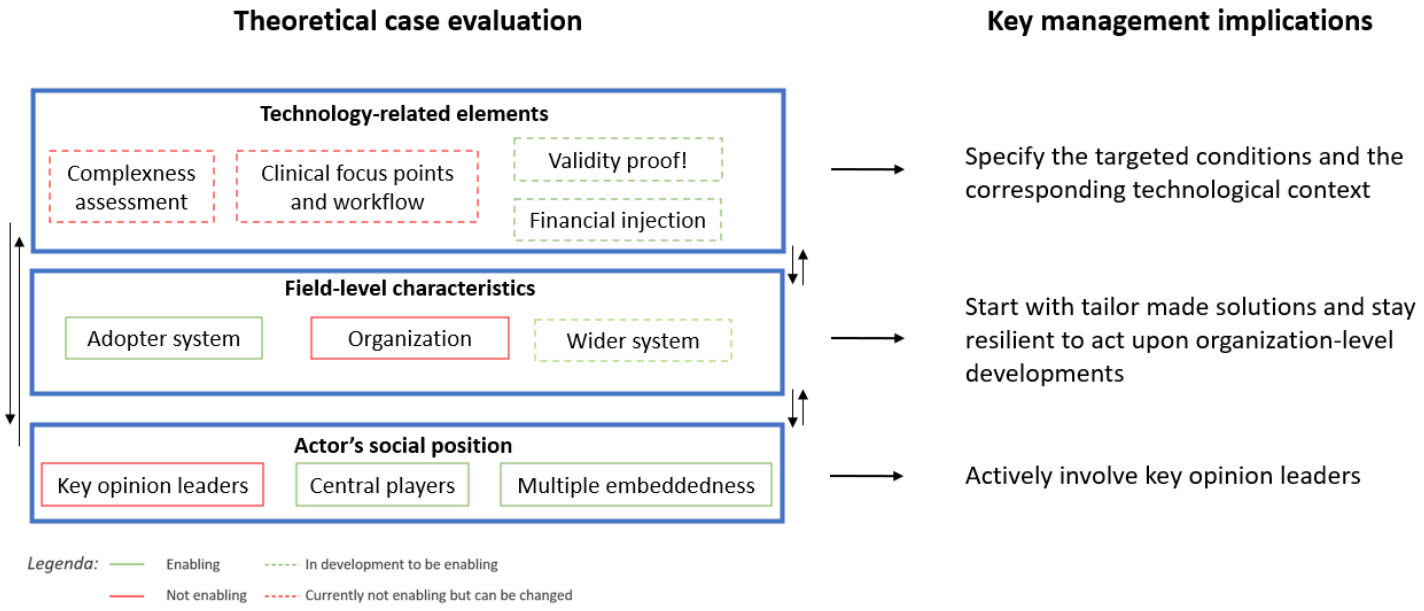
The results of this research indicate the opportunities for agents to act as an institutional entrepreneur to bridge the invention-innovation gap. The case studied in this thesis is FlowView Diagnostics. In the aim of contributing to the academic community, findings were mostly generalized. However, during the interviews, much in-depth information was gathered on the case itself. Closing the abductive research process, the conclusions of this thesis were applied as a managerial evaluation and implications for FlowView Diagnostics, based on the concluding integrated framework.

The case description was written during case selection, thus, before the research was conducted. During this research, FlowView Diagnostics grew as a company. It realized a financial injection that allows sufficiently for developments in the next two years. It hired a quality and regulatory expert in the team and involved the data scientists in the management team. To optimize the likeliness to successfully introduce technological and institutional change, the following implications should be considered (and a summary can be found in *figure 8)*.

- The company should specify its targeted disease. Currently, the algorithm focuses on minimal residual diseases for blood cancers. The term blood cancers however includes a set of targeted diseases, such as leukaemia or multiple myeloma. As highlighted in this thesis, these targeted diseases all use different markers, might have different levels of complexity, individual clinical focus points and a tailor-made workflow. To specify the technology-related elements of the algorithm, the company should specify one or multiple disease patterns, and define all the above to strategically choose the first innovation aim.
- FlowView Diagnostics has been realizing the financial resources. Until this point, they have sufficient resources for developments in the next two year. However, more funding should be generated to anticipate additional validity proofs and to facilitate organizational resilience in case of unexpected setbacks.
- Validity proof is a current focus point. Ideally, when more results show, they should be widely spread to make the field familiar with it. This can be done through the social position, discussed in the next point.
- FlowView Diagnostics already recruited a clinical expert and an IT expert. The further it gets in the development stage, the more important it becomes to connect to more than 1 clinical expert and look for a key opinion leader in the haemato-oncological diagnostics network. Over the past months, this has partly been done, however, active involvement of key opinion leaders is needed. An iterative collaboration between the medical key opinion leaders and the data scientist should be strived for, to decrease perceived risks and increase chances of acceptance on the adopter level.
- Besides the key opinion leader connections, the company thus far established a promising social position: it is already connected to central manufacturers and involved data scientists in its team to facilitate multiple embeddedness.
- The organizational level is expected to incur hurdles for innovation. The start-up should be closely following the latest developments in standardization to scout opportunities where it can move. In the current situation, the next step could be to identify the most widely used markers, hardware, and ICT systems, and create tailor-made solutions for those.
- Regarding the wider system level, it was found that although perceived as a barrier, the pieces of the puzzle can strategically be chosen to comply with the wider requirements. The company hired a quality and regulatory expert, who is familiar with the possible pieces of the regulatory puzzle. This is promising to bring the innovation forward.

Concluding, FlowView Diagnostics is aware of the system in which a technological innovation is embedded and shows the potential to create a thriving environment for AI innovation. Many theoretically promising steps have already been made, some are yet to be made. The points mentioned above are implied as a parallel process, to keep speed to market. Hopefully, this research can be insightful for the next steps, both for FlowView Diagnostics as well as for other initiatives, aiming to mature scientific inventions to clinical impactful innovations in the haemato-oncological field.

Figure 8: *Summary of case evaluation of FlowView Diagnostics and the corresponding management implications.*



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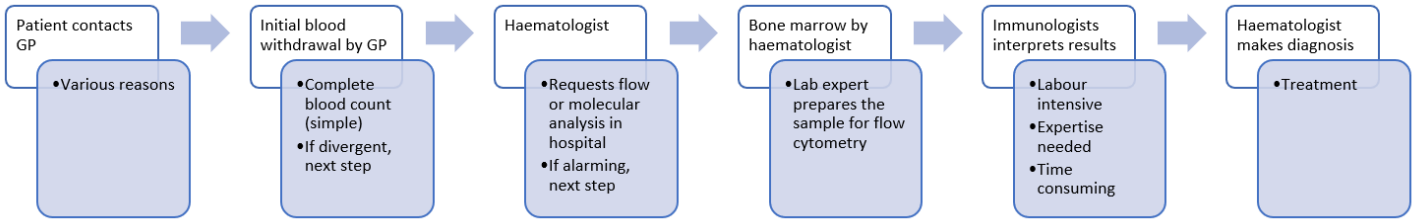
Appendix 1 - Description of the general diagnostic process of blood cancers

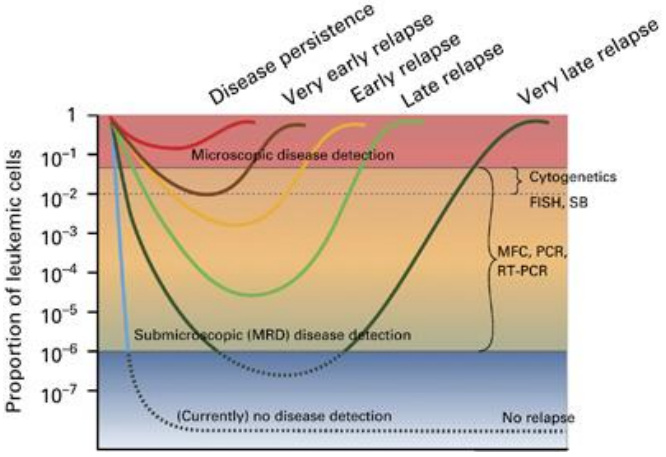
Blood cancers might be accompanied by symptoms or stay asymptomatic. Whenever a general practitioner (GP) suspects anything, he or she can withdraw a blood sample and request a complete blood count (CBC) test. If the results are alarming, the patient is referred to a blood specialist – the haematologist – who can request additional testing techniques such as a molecular analysis or a flow cytometry measurement (explained in *Appendix 2*). If additional results are alarming, a bone marrow sample is taken for in-depth analysis of the disease, using flow cytometry. The lab expert prepares the sample for the analysis, after which the immunologist interprets the results and communicates them with the haematologist, who diagnoses the patient. This workflow is presented in *figure A1*.

Figure A 1: *General workflow for diagnosis of blood cancer.*



When the treatment is working, a patient is said to be in remission when 'no' (<0.001 %) cancer cells can be detected in the blood and there are no symptoms. This is also called "No evidence of disease". However, due to the aggressive and progressive nature of the disease, malignant cells can advance and relapse. There are several scenarios for a relapse to occur, which can be seen in *figure A2.* The figure also indicates the analytical techniques used to detect the proportions of the cells, of which the MFC is most relevant for this thesis (further explained in *Appendix 2*).

Figure A 2: *The scenarios of cancer cells in the case of leukaemia. The figure was retrieved from the work of Buckley et al. (2013).*



One of the key challenges is to accurately monitor the chance of relapse with a minimum of patient discomfort. Currently, regular blood tests and check-ups are required. The frequency of these check-ups depends on the blood counts after initial treatment and the length of remission. Early after successful treatment, these check-ups occur typically once every three to nine months. This means the process in *figure A1* restarts at the bone marrow taken by the haematologist every period. If a relapse is detected, a new treatment cycle is started.

Appendix 2 - Description of multi-colour flow cytometry

A common analytical technique for the diagnosis of blood cancer is Multi-colour Flow Cytometry (MFC). This is a laser-based technique that counts and analyses the size, shape, and properties of individual cells within a heterogeneous cell population (Creative Diagnostics, 2020). The expression of cancer-associated cellular markers can be visualized by the binding of specific antibodies that are conjugated to a particular fluorophore. The presence of such fluorophore on a certain cell is then a measure of the likelihood of being a cancer cell. There are many fluorophores available, being fluorescent chemical compounds that can re-emit light upon excitation. The MFC technique enables to quantitatively detect marker expressions, among other cell characteristics, at the single-cell level (Folcarelli et al., 2018). MFC allows for both a biological and physical characterization of all cells at interest and can analyse cells at a detail of one in one million cells.

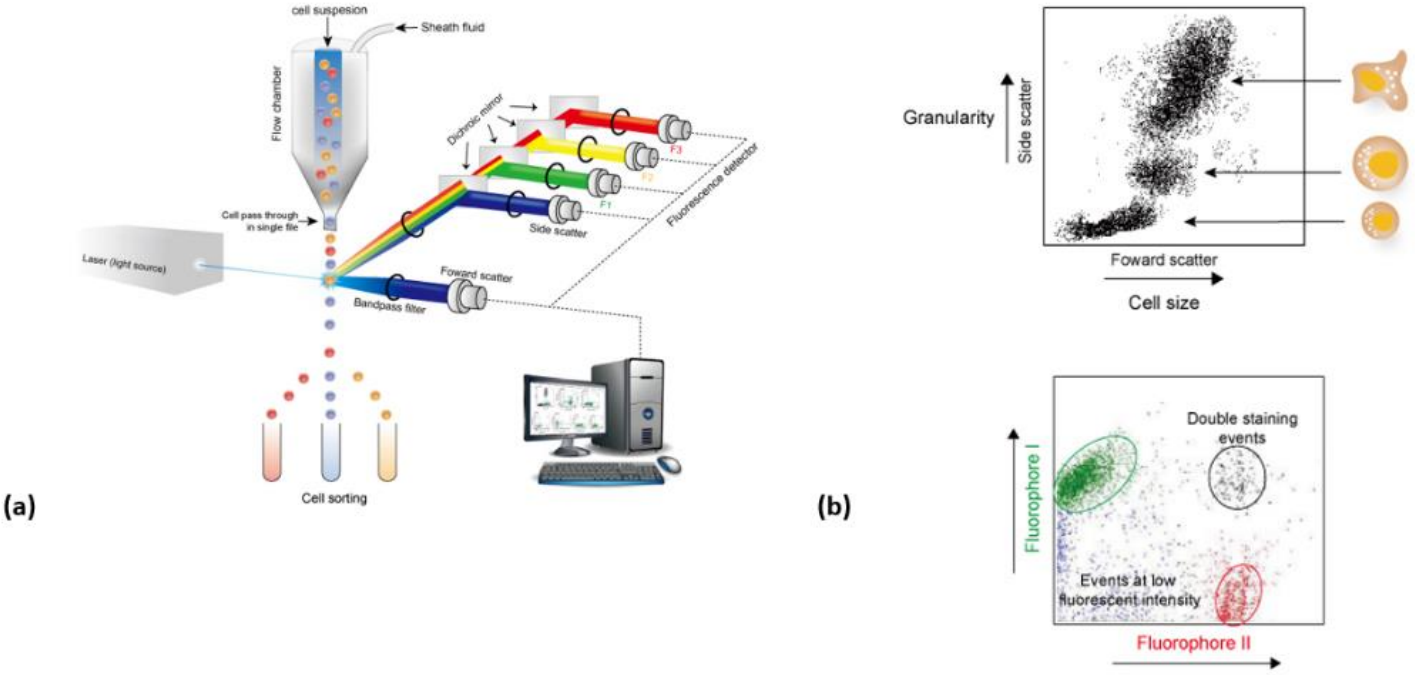
Fluorescence-based MFC currently allows for simultaneous measurements of more than 20 markers. The more markers are used, the more information about the cell will be displayed. Enormous amounts of data are being generated with each analysis (Folcarelli et al., 2018). However, a risk of using more markers is that this can cause irrelevant information masking relevant interpretation of the data, making it hard to notice the subtle nuances of the cells, as the obvious differences dominate the visualization. Therefore, per disease type, the relevant cellular markers are being selected and analysed. For example, for multiple myeloma, about eight cellular markers are being used (kappa, lambda, CD19, CD45, CD27, CD56, CD38 and CD138)).

During regular MFC data analysis, homogenous cell types of interest are selected by a method referred to as 'gating'. Manual 'multiple' gating on binary combinations of cell characteristics is the most widely used method. Experts need to establish qualitative thresholds in several bi-dimensional plots that cannot be mutually compared on the single-cell level. An example of this process can be seen in *figure A3*: (a) A sample of cells is fed into the flow cytometry machine. The flow chamber moves the sample into a narrow channel causing the cells to pass one by one through the laser. The detectors sense the light scattered by the cells. The computer transforms the data into plots that can be interpreted by the immunologist. (b) Two examples of plots are shown that can come out of the flow cytometry measurement. The first plot measures the forward and side scatter. Individual cells are divided based on size and granularity within the heterogeneous population of cells. The second plot divides the cells based on the colours they scatter; thus, the markers present on the cells. Potential gates are placed in different colours.

How the gates are placed, is decided by the immunologist. This results in a highly subjective and labour-intensive process: an individual sample with seven cellular markers would already require inspection of 21 bivariate plots – the first cellular marker is bi-plotted with the six others, the second with five others, and so forth until all combinations are represented in a bivariate plot. The more markers are measured, the more data is presented, but the more difficult it will become to manage the manual gating process. Other diagnostic methods[58] require different analytical techniques and have their own benefits and limitations, however, MFC is perceived to be the current golden standard for the setting studied in this thesis.

[58] More detail on other analytical techniques such as (real time) polymerase chain reaction (RT-PCR) for blood protein testing goes beyond the scope of this thesis, however, a good review can be found in the papers of Nunes et al. (2019), or in the work of Cruz et al. (2017).

Figure A 3: *Visualization of the MFC technique and examples of data output. The figure is retrieved from Creative Diagnostics (n.d.).*



Appendix 3 - Overview of attended events

Table A 1: *Overview of attended events.*

#	Date	Topic	Organization	Key speakers	Location
1	21-7-2020	Start:IP – From patent to market – Markus Pietzka	INiTS Universitäres Gründerservice Wien GmbH	Markus Pietzka - Program manager START:IP	Online
2	24-8-2020	Current Challenges of Digitalization in Healthcare Industry	2020 Digital Health Online Summit	Neshad Asllani - Head of the Board of Directors at Digital Clinic; Lead Ambassador at Telehealth and Medicine Today - Kosovo Chapter	Online
3	24-8-2020	Key components of a successful digital transformation strategy – June Leitch	2020 Digital Health Online Summit	June Leitch - Director of Operations and Transformation at National Health Service UK	Online
4	15-9-2020	AI-drieluik: Dokteren in de digitale wereld	Federatie Medisch Specialisten	Marleen Stikker - Director and founder of Waag Maneesh Juneja - Digital health futurologist	Online
5	17-9-2020	MedTechMeeting	MedTechPartners	Various speakers of the MedTech Partners community	Online
6	19-10-2020	Artificial Intelligence in Oncology: Advancing Science and Policy Virtual Symposium	Case comprehensive cancer center (CCCC)	Various speakers of the CCCC community	Online
7	19-10-2020	Is AI critical to improving efficiencies and outcomes in clinical trials?	Oracle Health Sciences	Jennifer Goldsack - Executive director digital medicine Nechama Katan – director of data science Pfizer Alex Zhavoronkov – founder and CEO Insilico Medicine Elvin Thalund – Director industry strategy, Oracle Health science	Online
8	24-11-2020	Toekomst van de Zorg	Health Valley	Harry van Goor - prof. dr. Is gastrointestinal surgery and innovation, Radboudumc René Bleeker - Directeur Project Bureau Bouwzaken, Radboudumc	Online
9	2-12-2020	AI in healthcare – how to turn promise into practice	Philips	Henk van Houten - CTO Tina Manoharan - Global Lead Data Science & AI	Online
10	14-12-2020	AI and DL in basic research and clinical practice in oncology	Oncode	Various speakers of Oncode / National Cancer Institute (NKI)	Online

Appendix 4 - Interview guide

A formal email was sent to the interviewee two days before the interview takes place.

Formalities

Dear Interviewee,

Thank you for participating in this interview. The interview will (anonymously) be used as data collection of my MSc Innovation Sciences thesis "From invention to innovation: An institutional perspective on AI developments for the haemato-oncological diseases".

The purpose of this interview is to explore the institutional dynamics during the development process of AI innovations, in specific of software developed for monitoring patient data. The case study that will be used in my master's thesis is FlowView Diagnostics. This company has developed an algorithm that compares the raw data coming out of the flow cytometry machine to the patient´s prior analysis and analyses automatically the differences for the case of detecting minimal residual disease (MRD) in haemato-oncological diseases. The results are presented in a simplified 2D-image, showing all the cell population. This leads to more accuracy in less time. The aim of this interview is to get a better understanding of the value drivers, way of use and desired improvements of all stakeholder groups.

Interview format

The interview questions will be semi-structured, which means that you are free to answer **openly and as detailed as you prefer**. If possible, please read through the questions beforehand (below) and have a look at the website of FlowView Diagnostics.

If there would be any question that you do not feel comfortable answering, that is of course fine. If there would be any unclarities, please do not hesitate to ask.

The interview will preferably be recorded to ease data analysis. If you would feel uncomfortable with this, please let me know. I would like to emphasize that interviewees will be mentioned as functional groups (such as, "flow cytometry experts", "clinical experts", "innovating agents" and "wider system stakeholders"), **ensuring that you and your answers remain anonymous**.

Thank you for wanting to participate and I am looking forward to speaking with you!

Interview questions

1. How and why do you use MFC or MRD data?

Prepare for use, use, receive the output?

2. What does the entire workflow look like?
3. Is the way of diagnosing MRD strictly regulated?
4. Where do you see the future of MFC/ MRD diagnostics?

Similar or different? Other potential? How useful is it? Fully accurate? Role of analysts and clinical experts? Ease of use?

5. Would you rather be open-minded or sceptical towards implementing AI in the field? Why?
6. Is the use of flow cytometry increasing or decreasing? Why?

Is there usage growth? Why (not)? Costs, alternatives, …

7. Do you expect any difficulties acquiring financial support for implementing this software? If yes, what kind?
8. What features are crucial for a technology/company that proposes a software support system for flow cytometry/ clinical support system for patient data analysis in MRD?

Trustworthiness? Big company or start-up? Experience in the field or from outside? Personal connection? Do you find your input in the development important?

9. What is key to consider a new technology for flow cytometry/ MRD diagnosis as legit?

What data would you need? What control should be there? Would you need insight into the underlying data? If yes, what underlying data?

10. Do you think the staff should go through any training processes in order to learn how to use an algorithm? Why?
11. Are there any alternatives that you are aware of?

Can also be different types of tests.

12. Do you think the data provided through flow cytometry can be presented more intuitively? If yes, how?

If yes, what parts of the data and how should it ideally be represented in your opinion? In a graph, in a 2D-image, stoplight format, …?

13. What elements of the data are most important?
14. Should all the data be always represented?

This can be specific per type of user. Should only the most important data be represented? Do you find it important to have easy access to all in-depth data?

15. What is the improvement that you are ideally looking for regarding the flow cytometry/ MRD analysis process??

Faster, easier data representation, fewer people involved, …?

16. How important is it for your organization that the innovation has an appropriate regulatory and privacy protection compliance in place? Do you think the requirements are adequate at the moment?
17. How important do you perceive the ability of a proposed innovation to easily adapt to change of systems?
18. Are there other contextual factors that might hamper or facilitate the usage of new algorithms?
19. Finally, what could be in your opinion main drivers and main barriers for the implementation of software for patient data?

Additional specific questions for the user stakeholders:

20. What is the nature of haemato-oncological diseases?
21. Are there particular socio-cultural factors related to this disease?

Additional specific questions for the agent stakeholders:

22. What are the key features?
23. What kind of knowledge does this innovation bring into play?
24. What knowledge is required to use the technology?
25. What is the technology supply model?

Appendix 5 - Overview of interviews

To make the information provided in this thesis as representable as possible, stakeholders from different institutions were included. Bot academic and non-academic hospitals were included, as well as big labs. The hospitals and labs included were: University Medical Centre Utrecht, Amsterdam University Medical Centre, Leiden University Medical Centre, St. Antonius Hospital, Albert Schweitzer Hospital, Saltro, Results Laboratorium. Furthermore, a balance in female vs male interviews was assured.

To guarantee the anonymity of the interviewees, all interviewees were given an acronym and only linked to the type of institute they are connected to.

Table A 2: *Overview of the interviews.*

Interview #	Stakeholder group	Acronym	Function	Institution	Format	Duration (min)
1	User - Clinical Expert	CE1	Internist-haematologist	non-academic hospital	Online	63
2	User - Flow Cytometry Expert	FE1	Medical Immunologist	academic hospital	Online	55
3	User - Flow Cytometry Expert	FE2	Postdoc in haematology/Oncology	academic hospital	Online	63
4	User – Clinical Expert	CE2	Internist-haematologist	academic hospital	Online	57
5	Wider system stakeholder – ICT systems	WSS1	Hospital ICT system manager	non-academic hospital	Online	50
6	Wider system stakeholder – AI innovation expert	WSS2	TWIHC member & Laboratory specialist clinical chemistry	Laboratory	Online	75
7	User - Clinical Expert	CE3	Internist-haematologist	non-academic hospital	Online	73
8	User – Flow Cytometry Expert	FE3	Researcher Drug Development	academic hospital	Online	58
9	Wider system stakeholder – Manufacturer	WSS3	Global Marketing Manager Flow Cytometry	Beckman Coulter	Online	57
10	Innovating Agent – Flow Expert	IA1	Professor	academic hospital	In-person	90
11	Innovating Agent – Developer ICT	IA2	ICT	Amatis	Online	40
12	User – Flow Cytometry Expert	FE4	Laboratory specialist clinical chemistry	non-academic hospital	In-person	90

13	Wider system Stakeholder – Digital innovation for cells	WSS4	Innovator of AI for haematology and cell visualization	Laboratory	Online	50
14	User – Flow Cytometry Expert	FE5	Laboratory specialist clinical chemistry	non-academic hospital	Online	56
15	Wider system stakeholder – Manufacturer	WSS5	Global Marketing Manager Flow Cytometry Software	Beckman Coulter	Online	60
16	Innovating Agent – Developer – CEO	IA3	Product management and funding	FlowView Diagnostics	In-person	75
17	Innovating Agent – QCA manager	IA 4	Quality and regulatory control	FlowView Diagnostics	In-person	60
18	User – Clinical Expert	CE4	Internist-haematologist	academic hospital	Online	60

Appendix 6 - Initial coding scheme

Table A 3: *Initial coding scheme.*

Variable/domain	A priori element (code)	Description
Technological context		
4.1 Technology-related elements		
4.1.1 Condition	Nature of condition	The clinical context in which the innovation is implemented
	Suitability of technology	Elements of the condition that are relevant for the suitability of the technology
4.1.2 Value proposition	Downstream	Considerations whether the technology is worth developing - Influencing technology appraisal
	Upstream	Considerations whether the technology is worth developing - Influencing investment decisions and logic of financial markets
4.1.3 Technology	Material features	Technology-related elements influencing usability, appropriateness, and dependability
	Knowledge generated	The knowledge that is generated by the technology
	Knowledge to use	The knowledge base needed to use and support the technology
Institutional context		
4.2 Field-level characteristics *Heterogeneity of institutions and degree of institutionalization*		
4.2.1 Adopter system	Functions	Identification of the various users
4.2.2 Organization	Capacity and readiness to innovate	Institutional findings of hospital or laboratory, and connections between them
	Ease of adoption decisions	Institutional findings of hospital or laboratory, and connections between them
	Clinical workflow	Containing elements such as assay selection, marker expression, interpretations, and the purposes of flow analysis
4.2.3 Wider system	Political context	Indication of health policies or initiatives influencing the field
	Regulatory context	Established legislative and regulatory elements
	Professional bodies	Influential professional bodies
4.3 Actor´s social position		
	Legitimacy requirements	What is needed for the innovation to be required as legit
	Attitude on AI	Perception on AI

Appendix 7 - Final coding scheme with examples of operationalization

Table A 4: *Final coding scheme with examples of operationalization.*

Variable/domain	Codes	Description	Reference example
Technological context			
4.1 Technology-related elements			
4.1.1 Condition	Nature of condition	The clinical context in which the innovation is implemented	"Some disease entities might be fit earlier for computational residual disease monitoring. For example, the successes of monitoring multiple myeloma or acute lymphatic leukaemia's, they come from the fact that often these phenotypes that are recognized are just more easy to interpret and suffer less from heterogeneity so that's why for example the algorithms in development are working less well for acute myeloid leukaemia patients than they do with multiple myeloma samples." - FE2
	Suitability of technology	Elements of the condition that are relevant for the suitability of the technology	"In more complex fields like leukaemia and lymphoma, you see a variety of sample types, due to the heterogeneity of questions that can be answered. Also moving towards personalized medicine, with specific sample combinations per patient. Impossible to standardize and automate that - have no idea what the customer wants to look for. In the end, the algorithms expect a cell population at a certain position."- WSS3
4.1.2 Value proposition	Downstream	Considerations whether the technology is worth developing - Influencing technology appraisal	"We need algorithms that are less prone to mistakes and make faster diagnosis."- FE1
	Upstream	Considerations whether the technology is worth developing - Influencing investment decisions and logic of financial markets	"An idea does not become big without a major monetary injection." – WSS2
4.1.3 Technology	Material features	Technology-related elements influencing usability, appropriateness and dependability	"Garbage in, garbage out."- FE4 *OR* "You need a simplified output for a specific target audience and then you always need to be able to go back to the detailed results for specific cases." – FE2
	Knowledge generated	The knowledge that is generated by the technology	"There is a lot of tension between on the one hand the rationale, objective information of the algorithm, versus the experience-driven outcomes of a clinician." – CE1
	Knowledge to use	The knowledge base needed to use and support the technology	"People will always need additional education, to understand how to use and how to interpret the data" – FE4

	Competing developments	Information on other AI developments with similar purposes	"Hardware manufacturers are now also developing software, all having slightly different features. We use the software connected to our hardware. And when they see external developments that fit well into their portfolio, they buy those." – FE4
	Complementary hardware	Considerations on hardware the algorithm should work with	"Over the past decades, hardware started to evolve. More lasers were added, and detecting 5, 20 and now even 50 channels in parallel. The complexity of the panels has evolved. However, on the analysis side, we are still doing the same thing we did 20 years ago, where people are looking at 2-dimensional dot plots. Hence, hundreds of them"- WSS5
	Legitimacy requirements	What is needed for the innovation to be required as legit	"So procedures need to prove themselves, you require extensive validation of the algorithmic approaches versus the conventional approaches."- FE2
Institutional context			
4.2 Field-level characteristics *Heterogeneity level of institutions and degree of institutionalization*			
4.2.1 Adopter system	Functions	Identification of the various users	"People often take pride in what they are doing. So whenever you come in with a product that claims to automate it away, it might feel threatening."- WSS5
	Key opinion leaders	Members who opinion is highly valued by others	"The facilitators for such innovation are for sure the clinical experts. Also the flow experts. If they are excited, it might be implemented." – CE3
4.2.2 Organization	Capacity and readiness to innovate	Institutional findings of hospital or laboratory, and connections between them	"Labs that are less close to the bleeding edge of science, I think it will be harder to get their acceptance. They've always done it a certain way, so why change something now." – WSS5 *or* "In Europe, by tradition, every hospital has its own method and micro combination and approach. If you learn a method from your superior, that is what you do. There is a lot of tradition and high reluctancy to change the highly standardized solutions." – WSS 3
	Ease of adoption decisions	Institutional findings of hospital or laboratory, and connections between them	"We have a flat structure so it is easy to make a decision. I have 4 colleagues. If I am enthusiastic, my colleagues will probably be too. In academic centres you have to go through the head of the departments, experts and staff-meetings, so that's more complicated." – CE3
	Clinical workflow	Containing elements such as assay selection, marker expression, interpretations and the purposes of flow analysis	"In the workflow, there is limited consensus. Small groups might form that then align on a consensus panel for a particular application, but we are very, very far away from standardization." – WSS 5

4.2.3 Wider system	Political context	Indication of health policies or initiatives influencing the field	"Luckily, the government is acknowledging that things need to change. They are now introducing subsidiary programs and acceleration programs." – WSS1
	Regulation	Established legislative and regulatory elements	"Regulations can be a big issue. Start even with our own medical ethical committees within our Institute or the privacy laws that we have to comply with. Such regulations make it more difficult to share data, to work on data, to collaborate on data processing and analysis. So then we're not even at the stage where we have developed a method and need to comply with drug authority regulations or governmental regulations." – FE2
	Professional bodies	Influential professional bodies	/
	Future outlook	Perceptions of the future outlook of the field	"Their perception is that clinical MFC will not die. It will not be replaced by other molecular technologies, especially for haemato-oncological diseases - you need a differentiator on the cell level. Flow definitely is the method of choice. For other applications such as COVID, might be better with other technologies."- WSS3
4.3 Actor´s social position			
	Attitude on AI	Perception on AI	"In the medical sector, we are mainly conservation. We like to first see others try, and if it works well, we will copy, adapt and paste." - WSS1
	Resilience	The ability to constantly adapt the technology to changes in the field	"Every company gets what it deserves. So if you are flexible and agile to constantly adopt to new developments, that helps a lot."- IA4

Appendix 8 - Inter-coder reliability check using Fleiss' kappa

Table A5 shows the codes given by each researcher. *Figure A4* shows the overall agreement value, being 0,828. The Fleiss' kappa was calculated in SPSS Statistics, showing a value of 0,828. This can be considered highly reliable.

Table A 5: *Overview of the inter-coder reliability check process. The table presents the codes given by other researchers.*

#	Statement	Researcher 1 (author)	Researcher 2	Researcher 3
1	"AML is a very heterogeneous disease so perhaps for other diseases entities, the hurdles might be smaller." - FE2	Suitability of technology	Suitability of technology	Suitability of technology
2	"If we look at flow cytometry in the past decades, or couple of decades, first the hardware started to evolve. Manufactures added more lasers, people could detect 5 – 10 – 20 channels in parallel. Now with mass cytometry, this can go up to 50. So the complexity of the panels has evolved. But first, it was the hardware. Then companies started to develop the reagents, labs slowly adopted higher marker panels. And on the analysis side, we're still doing things pretty much the same way we did them 20 years ago, where people look at 2-dimensional dot plots. Hence, hundreds of them." - WSS5	Complementary hardware	Wider system - General	Complementary hardware
3	"I would be happy if we would have an algorithmic approach that is very accurate and is just able to do the job." - FE2	Downstream value proposition	Downstream value proposition	Downstream value proposition
4	"We work with GLIMS, a lab software, but there are many different systems out there and they all use different languages." - WSS1	ICT systems	Material features	Organization - Clinical workflow
5	"The facilitators are the clinical experts and lab experts." - CE3	Key opinion leader	Key opinion leader	Key opinion leader
6	"What you need, is people who will push the technology through in their organizations." - FE5	Key opinion leader	Key opinion leader	Key opinion leader
7	"Then only the medical technologists can transfer the first data to the physician and the normal line is that there are two independent technicians who analyse the data and if they agree, then it can be authorized by the medical immunologist." - FE1	Adopter system - Function	Adopter system - Function	Adopter system - Function
8	"All regulatory norms come from different organizations within countries and between countries - IA 4	Wider system - Regulation	Wider system - Regulation	Wider system - Regulation
9	If it is really innovative, clinical experts pick it up at congresses and communicate it to their organizations." - FE5	Key opinion leader	Key opinion leader	Key opinion leader

10	“A quality plan is a worldwide requirement for any medical device to reach the market.” - IA4	Wider system - Regulation	Wider system - Regulation	Wider system - Regulation
11	“I think there is a lack of understanding at clinical expert of how algorithms work, which is needed for correct use.” - WSS2	Technology - Knowledge needed to use	Actor´s attitude on AI	Actor´s attitude on AI
12	“In our department, we use the DIFA software or Infinicyt.” - FE1	Technology - Competing developments	Technology - Competing developments	Technology - Competing developments
13	“Every company gets what it deserves. If you are flexible and agile enough to adapt to the constantly developing environment, that's a big pro.” - IA 4	Resilience	Resilience	Resilience
14	“In the workflow, there is limited consensus. Small groups might form that then align on a consensus panel for a particular application, but we are very, very far away from standardization.” - WSS 5	Organization - clinical workflow	Organization - clinical workflow	Wider system - Future outlook
15	“For labs that are less close to the bleeding edge of science, I think it will be harder to get their acceptance. They have always done it a certain way, so why change something now.” - O5	Organization - Ease of adoption decisions	Organization - Ease of adoption decisions	Organization - Ease of adoption decisions
16	“People often take pride in what they are doing. So whenever you come in with a product that claims to automate it away, it might feel threatening.” - WSS5	Adopter system - Function	Adopter system - Function	Adopter system - Function
17	“We need algorithms that are less prone to mistakes and make a faster diagnosis.” - FE1	Downstream value proposition	Downstream value proposition	Downstream value proposition
18	“In more complex fields like leukaemia and lymphoma, you see a variety of sample types, due to the heterogeneity of questions that can be answered. Also moving towards personalized medicine, with specific sample combinations per patient. Impossible to standardize and automate that - have no idea what the customer wants to look for. In the end, the algorithms expect a cell population at a certain position.” - O3	Suitability of technology	Suitability of technology	Suitability of technology
19	“Some disease entities might be fit earlier for computational residual disease monitoring. For example, the successes of monitoring multiple myeloma or acute lymphatic leukaemia’s, they come from the fact that often these phenotypes that are recognized are just easier to interpret and suffer less from heterogeneity so that is why for example the algorithms in	Nature of condition	Nature of condition	Nature of condition

	development are working less well for acute myeloid leukaemia patients than they do with multiple myeloma samples." - FE2			
20	"A lot of developments are taking place in the field, so the advancements of the algorithmic approaches basically come from the increased technical options of the flow cytometry so beginning with mass cytometry but also in fluorescence cytometry, it's now possible to measure more and more parameters. So that will increase the value of the technique of course and with the advent of those additional techniques, you need software to analyse data, because you cannot do that in the classical bi-variate strategy anymore." - FE2	Complementary hardware	Complementary hardware	Complementary hardware
21	"The quality is really the most important." - FE1	Legitimacy	Legitimacy	Legitimacy
22	"My main point is that if you refuse to use digital technologies, you will have no right of existence anymore. Hospitals that do use it will be faster, better, and more cost-efficient." – WSS1	General adopter system: Attitude towards AI	Legitimacy	Wider system - Future outlook
23	"What happens as a follow-up protocol is a question mark. In an academic hospital, everything can be tested. In a non-academic hospital, we are much more critical." - CE3	Organization - general	Organization - general	Organization - general
24	"So, procedures need to prove themselves, you require extensive validation of the algorithmic approaches versus the conventional approaches." - FE2	Legitimacy	Legitimacy	Legitimacy
25	"We have collaborations between multiple hospitals so you could expect us to work together. But in the end, everyone has their own priorities." - WWS1	Organization - general	Organization - general	Organization - general

Figure A 4: *Fleiss' kappa*

Fleiss Multirater Kappa

[DataSet1]

Overall Agreement[a,b]

	Kappa	Asymptotic Standard Error	Asymptotic z	Asymptotic Sig.	Asymptotic 95% Confidence Interval Lower Bound	Asymptotic 95% Confidence Interval Upper Bound
Overall Agreement	,828	,031	26,705	,000	,826	,830

a. Sample data contains 25 effective subjects and 3 raters.

b. Rating category values are case sensitive.