A FEMINIST ENGAGEMENT WITH SYSTEMS MEDICINE

By

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Dissertation

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Abstract

My PhD project examines systems medicine from a philosophy and sociology of science approach. Based on my fieldwork at the Institute for Molecular Medicine Finland (FIMM), I describe systems medicine research and its relations to personalised medicine. The broader aim of the study is to investigate what it would mean to form feminist engagement with systems medicine. I will do this by analysing the ways in which categories such as gender are considered in molecular medicine research. This study contributes to feminist science studies and feminist new materialism. In feminist new materialism, engaging with new approaches in life sciences is seen as a beneficial undertaking when reconsidering the role of materiality in feminist theory because systems approaches avoid reductionist biological explanations. However, little attention has been given to the ways in which systems approaches are implemented in medical research. My research does not offer an evaluative analysis of FIMM's research, but shows that focus on gender in molecular medicine research can help to further question the possibilities of researching gender differences with big data approaches. The examination of present-day practices helps to understand the epistemological challenges in explaining gender differences in diseases as such research requires large quantities of standardised biological and environmental data. Moreover, gender analysis helps to see how studying gender differences in diseases is linked to the goals of personalised medicine. I emphasise that in personalised medicine initiatives the future of healthcare is focused on individuals' own efforts in disease prevention whereas a feminist approach would also emphasise societal inequalities as the basis for gender differences in diseases. My research shows that feminist engagement with systems medicine can help to better contextualise systems medicine research as well as stress the importance for feminist scholars to consider the current possibilities to address gendered differences in data-centric research.

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Introduction

"Cancer cells? Why would anyone want to store those?"

A loaded silence filled the room. I noticed the face of the laboratory technician, who I was shadowing that day, stiffening. She did not reply but turned her back to the repairman, who had come to fix the air-conditioner system at the room used to store patient samples, and continued to search for the ovarian cancer sample we had come to collect. I understood why the technician was annoyed by the repairman's reaction and, what is more, I noticed myself sharing her frustration. Did the repairman not realise how central those samples were for the study of cancer? I had spent already two months at the Institute for Molecular Medicine Finland (FIMM), interviewing researchers about their work and observing their daily research practices. All my interviewees, ranging from group leaders to doctoral students, had emphasised the value of subcategorising cancer profiles to ensure better individual care. Moreover, all the laboratory technicians I met prided themselves on having established functional research protocols ensuring standardised cancer cell research. Having observed this, the repairman's reaction towards cancer cells seemed inconceivable.

Later the same day, as I was writing down the incident, I suddenly felt nauseous. I remembered a day half-year earlier, when I first heard of my father's diagnosis. I felt like I could grasp the repairman's words for the first time: to understand the horror that the word "cancer" can hold. A word that can leave little room for anything else. From that moment on, what became inconceivable was not the repairman's intuitive shock but my own initial reaction to his words. I imagined how the simple procedure, quotidian for the technician, might have been experienced by the repairman. I could not help thinking how this event showed the striking differences of reactions that people can have towards cancer cells—seeing them either as objects of innovative research or as tokens of frightening lived experience.

In social sciences, this distinction in perception has been described as a difference between illness and disease. While disease is a medical term, used to bring together a set of diagnostic principles and treatment guidelines, examining illness shows patients' individual experiences in living with a disease. Annemarie Mol states in her book *The Body Multiple* (2002) that distinguishing illness from disease was central for the development of the field of medical sociology as it allowed social scientists to analyse medical practices, which for a long time had remained only tied to medical profession.[1] She traces the history of medical sociology to Talcott Parsons' book *The Social System* (1951), which argued that illness is "partly biological and partly socially defined."[2] By emphasising the need to record how illness is experienced, social scientists after Parsons have underlined their separate take on the world of medicine, without questioning the expertise of physicians to talk about diseases. However, as Mol writes, gradually social scientists "started to worry about the power a strong alliance with physical reality grants to doctors."[3] Hence, more social scientists started to take doctors as their research subjects, questioning how their perspective on disease was formed, rather than seeing medical descriptions of diseases as all-encompassing physical realities.[4]

Mol, nevertheless, sees a problem in this turn that social science has taken towards medical sciences. The issue, she underlines, is that by focusing on collecting different viewpoints in relation to disease, the "body's physical reality is still left out."[5] The "disease", in other words, remains a concept that grounds all accounts of it but is itself left unscrutinised. Thus, Mol suggests a third step for social scientists studying medicine, consisting of "foregrounding practicalities, materialities, *events*" so that "'disease' becomes a part of what is done in practice."[6] In her book, Mol seizes this challenge to overcome disease/illness dichotomy

[1] Mol 2002, 9.
[2] Parsons 1951, 431, cited in Mol 2002, 10.
[3] Mol 2002, 9.
[4] Ibid., 10.
[5] Ibid., 11.
[6] Ibid., 13.

by investigating how patients' experiences, treatment, and study of atherosclerosis intertwined in a Dutch hospital. However, her approach is not tied to collecting all different perspectives related to atherosclerosis, be them from patients, nurses or doctors, but she writes about interactions in hospital settings that give the disease different meanings in different events.

The need to challenge illness/disease dichotomy in social sciences is central for my research. This emphasis might seem surprising given that I did not conduct fieldwork at a hospital where the relationship between disease and illness is constantly renegotiated. Instead, my dissertation is based on a fieldwork in a research institute specialising in molecular medicine (FIMM). I have not included patient experiences or observed how the studied diseases are treated in a hospital. Most of my interviewees had no contact with patients. Still, the division between illness and disease, which seemed indisputable in the short encounter between the technician and the repairman, tells little about how FIMM's researchers navigate between the world of illness and disease. For example, a researcher at FIMM, who also worked as a clinician, told me how the months she focuses on research are also mentally distinct from the time she operates as a clinician. She described research time as more "positive", including possibilities to get excited about research findings, whereas in a hospital cancer was always present as a heavy burden of meeting patients and their loved ones and seeing them go through cancer treatment. However, rather than seeing these two worlds apart, she underlined her abilities to help other researchers in her group to be aware of what kinds of issues clinicians must face when deciding how to treat a patient. The contributions that people such as this clinician can give to medical research is central for FIMM's operation, as the institute is dedicated to consider new ways to form an active link between basic research and clinical work.

The reason why I wish to emphasise the relevance of questioning the illness/disease dichotomy is because my research aims to offer a feminist approach to contemporary molecular medicine research, focusing especially on systems medicine research. Systems medicine is one

of the research focuses at FIMM, aiming to develop ways to bring patient specific molecular-level information to disease treatment and prevention. The focus in FIMM's systems medicine specialisation is on cancer research. Their aim is to develop individualised approaches to cancer treatment, formed in close collaboration with the neighbouring hospital. As systems medicine places patients' individual differences at the central stage of the research, it gives an ample possibility to consider how the link between personal differences in disease emergence and treatment and the aim to understand basic mechanisms of diseases is managed in molecular medicine research. In order to consider the relevance of such approaches for feminist research, my main research question is how new approaches in molecular medicine research can help to also account for gendered differences in disease emergence and treatment outcomes.

It is crucial for feminist scholars to engage with new medical research approaches, often labelled as personalised or individualised medicine, because they are envisioned to profoundly transform healthcare practices. FIMM's research is a part of larger changes happening in the field of life sciences. Nikolas Rose states in his book *The Politics of Life Itself* (2007) that although medical practices were long based on the "molar" level of bodies, meaning visual, tangible body consisting on limbs, organs and so forth, today's biomedicine operates in a different level of the body—the "molecular" level.[7] The molecular vision of the body has not only changed the way in which biology is understood but it has also changed the way in which the potentialities of biomedicine are viewed. Rose argues that biomedical practices have enabled people to better control their biology rather than be completely defined by it. What, thus, becomes central in the "age of biological control", according to Rose, is that biology itself does not limit human ambitions.[8] In medical research, the increasing focus on molecular-level mechanisms of diseases has introduced new possibilities to personalise disease treatment and prevention.

[7] Rose 2007, 11–13.
[8] Ibid., 16–17.

Possibilities to personalise medical care are based on technological developments, making it possible to generate and integrate large datasets in biomedical research. In biological research, new technological possibilities have led to forming of a new research field, called systems biology, which aims to account for the complexity of biological organisms in research. Systems biology approaches are often labelled as data-centric approaches because big data resources are foundational to mapping complex biological functions.[9] Systems biology approaches are at the heart of novel approaches in molecular medicine research as large amount of data gained from individual patients is used to study individual specific disease mechanisms. These approaches gain medical relevance because this molecular-level information is then used to design treatment best suited for individual patients as well as to create a comparative analysis that can help to stratify molecularly similar patients within a disease.

The terms such as systems medicine, personalised medicine, precision medicine, 4P medicine, in silico medicine, and individualised medicine—all which represent possibilities to implement big data approaches in medical care—do not only describe changes in treatment planning but also imagine a far-reaching transformation in the ways in which future healthcare in organised.[10] While personalised medicine is a relatively new field, its proponents, such as Leroy Hood, imagine a quick change that systems approaches can bring to healthcare practices. Ultimately, he envisions, healthcare actions would be more concentrated on active prevention, shifting the healthcare focus from treating diseases to optimising wellness. He writes optimistically that "in 10 years each patient will be surrounded by a virtual cloud of billions of data points, and we will have the tools to reduce this enormous data dimensionality into simple

[9] See Kastenhofer 2017 and Leonelli 2016.

[10] The terms 'systems medicine', 'personalised medicine', 'systems 4P medicine', 'precision medicine', and 'individualised medicine' are sometimes used as synonyms, sometimes to highlight different aspects of these approaches, some of which do not necessarily refer to systems approaches in medical research. I use these terms interchangeably to represent broader changes envisioned to take place in healthcare when big data approaches, including systems approaches, are applied to medical decision making. However, when I talk about "systems medicine research", I specifically refer to the ways in which systems biology approaches are applied to present-day biomedicine.

hypotheses about how to optimize wellness and avoid disease for each individual."[11] Even if other scholars would have less ambitious or rapid predictions for the year 2023, it is unquestionable that systems approaches will affect medical practices in the future.[12]

My research investigates present-day molecular medicine research practices to open discussion of a possible feminist engagement with the changes taking place in biomedicine. Examining systems medicine research is important as it can help to shed light on the extent of changes now happening in biomedical research and its connection to clinical practices. As mentioned previously, my main research question is how systems medicine can account for gendered differences in disease emergence and treatment outcomes. This might seem as an odd question as FIMM's systems medicine research is not focused on studying gender differences and, thus, these questions are outside of the scope of FIMM's daily research. Nevertheless, there are two reasons why examining systems medicine research is interesting and relevant for feminist scholars.

Firstly, the growing emphasis on accounting for individual differences in diseases leads to a question of the basis of these differences. As the proponents of gender medicine argue, personalised medicine has failed to account for the fact that in some diseases the differences within a patient group are clearly gendered, showing a striking gender discrepancy in clinical data in the number of patients or the treatment outcomes.[13] Thus, it is important to investigate reasons behind such gender differences. Gender medicine initiatives highlight that it is important to consider both biological and social reasons when studying gendered differences in clinical data.[14] It is, then, interesting to question to what extent can current biomedical research study the basis of gendered differences in clinical data. Answering these question is not straightforward as gender differences are not studied at FIMM. FIMM's systems medicine

[11] Hood 2013, 1.
[12] See, for example, Auffray et al. 2016 and Green 2017
[13] See, for example, Regitz-Zagrosek 2012.
[14] See Klinge 2007, Oertelt-Prigione 2012, and Schiebinger 2012.

research operates in a molecular level with pilot studies focusing on establishing ways to account for individual differences in drug treatment. As FIMM's goal has been on establishing a basis for individualised treatment, it has not operated in the level of categories such as gender. Still, gendered analysis, I argue, offers a fruitful foundation to consider FIMM's research's relation to larger changes happening now in biomedical research as it directs the analytical focus to questioning the meaning of "personal" in personalised medicine.

Personalised medicine is focused on basic disease mechanisms, which, as the proponents of gender medicine stress, leaves a lot of aspects outside of the research scope. As Peter Langkafel has noted, the term "personalised medicine" has raised criticism in some as personalised medicine does not address individuals' self-determination, or other elements that are often used to define the concept of "personal", but concentrates on molecular-level biological mechanisms.[15] This clarification is important when thinking of the relevance of categories such as gender in molecular medicine research. How and to what extent can molecular-level analysis reflect the lived realities of humans when planning preventative measures in healthcare? While molecular-level research can be centred on investigating biological mechanisms, this question becomes essential when thinking of ways to apply molecular-level information in diagnostic practices and preventative measures. The proponents of gender medicine stress that personalised medicine does not make gender medicine irrelevant as gender seems to remain an independent risk factor in large datasets.[16]

However, it is difficult to evaluate the possible impact of personalised medicine to healthcare, as it largely consists of pilot studies and future goals at the moment. Thus, if one wishes to gain a better understanding of the changes taking place in biomedical research and consider how systems approaches can be brought to medical practices, it is imperative to examine the current systems medicine research. Systems medicine research done at institutes

[15] Langkafel 2015, 26–27.
[16] Regitz-Zagrosek 2012, 4.

such as FIMM could be a stepping stone towards personalised medicine but not its representation. As Langkafel states, current research approaches are largely invested in pharmaceutical collaborations, aiming to benefit production of precision drugs by subcategorising patient groups based on their molecular profiles. This is also the case with FIMM. A "true" individualised or personalised medicine, on the other hand, would "suggest a therapy that is precisely tailored to the individual being treated."[17] Examining systems medicine research, hence, requires questioning how its current practices are linked to the broader goals imagined in personalised medicine literature without equating them.

I argue that the category of gender is a useful tool to address possibilities and limitations seen in ongoing research. While FIMM's systems medicine research does not currently include the study of gendered differences, thinking how molecular medicine research is linked to categories such as gender will help to open discussion about the relationship between present-day biomedical research and societal change in healthcare organisation. The usefulness of gendered analysis is owing to the murkiness of the concept of "gender". Gender is a basic category in clinical statistics and as such commonsensical to social scientists and medical professionals alike. However, the category blurs when trying to explain the reasons behind recorded gender differences in clinical data because the reasons behind statistical differences in the amount of male and female patients can contain both biological and social aspects, or sex and gender differences as they are often separated in medical literature. Asking how consideration towards possible gender differences in diseases could be included into systems medicine research is, hence, helpful when examining the new possibilities opened by systems approaches in medical research and their current limitations.

The second reason why systems medicine research is interesting for feminist scholars is its origins in systems biology. Systems biology is one of the examples used in feminist new

[17] Langkafel 2015, 27.

materialist scholarship to exemplify new approaches in life sciences that aim to incorporate biological complexity better into the research.[18] The term "new materialism" was launched both by Rosi Braidotti and Manuel DeLanda independently in the 1990s to claim a move away from the nature/culture dichotomy in social science. Feminist scholars have seen new materialism as a way to newly consider the role of materiality in feminist theory.[19] As Iris Van Der Tuin and Rick Dolphijn emphasize in their article "The Transversality of New Materialism" (2010), the aim of new materialism is to formulate a cultural theory that would not emphasise the role of culture over materiality, by seeing it as a discursive creation, nor support a positivist natural science view of matter, that could be used as a basis for essentialist and determinist argumentation. Instead, they highlight the need to talk about meaning production as material-discursive, meaning that while social relations do shape the way in which materiality is perceived, matter itself also takes active part in its materialisation.[20]

Diana Coole and Samantha Frost state in the introduction of the book *New Materialism* (2010), that new approaches in natural science, systems biology included, can help feminist scholars to theorise the process of materialisation as a fluid, open-ended and dynamic process. They point out that especially since the completion of the Human Genome Project (HGP) the study of organisms has increasingly implemented the vision of the body as a complex system that is also affected by its environment. [21] This was because the HGP revealed that humans have a relatively low number of genes in the human body, which challenged the idea that diseases, as well other human conditions, could be explained as a function of a distinct gene. Systems biology, as Evelyn Fox Keller points out, functions as an umbrella term to describe new approaches in biological research that, instead of focusing on particular units in the body such

[18] Coole & Frost 2010, Blackman 2016.
[19] See for example Alaimo & Hekman 2008, Braidotti 2000 & 2002, Coole & Frost 2010, DeLanda 1996 and Dolphijn & Van der Tuin 2010 and 2012.
[20] Van Der Tuin & Dolphijn 2010, 153–159.
[21] Ibid., 15–18.

as genes, study organisms as complex systems, which are also open to environmental factors.[22] This approach in medical research can be seen as a great importance for feminist thinkers since it complicates possibilities for simplified explanations of diseases that are often connected with the existing social and cultural connotations of gender, race and heredity. By highlighting scientific research which studies an organism as a part of, and influenced by, its environment, feminist scholars have argued that more complex view of the human body can challenge cultural readings connected to the simplified account of genetic determinism.[23]

Thus far, systems medicine research, despite its basis on systems biology, has not been examined in feminist scholarship. Instead, the attention of recent feminist new materialist scholarship has largely been on the study of epigenetics. This is understandable as the field of epigenetics, which aims to examine environmental factors influencing biological functions, can be easily linked to gender specific questions. For example, Lisa Weasel has considered the ways in which epigenetics can be used to stress the importance of feminist intersectional analysis, showing how social inequalities can shape physiology,[24] and Sarah Richardson has showed how epigenetics is largely based on questioning maternal-foetal interaction.[25] The field of epigenetics gives feminist scholars resources to question how gender is implemented in the research and how applying research information is directed to male and female bodies differently. The importance of epigenetic risk factors are also added to gender medicine literature, making the examination of the field a valuable addition to feminist science studies.

Compared to epigenetics, the relevance of systems medicine research for feminist scholarship can seem questionable as an investigation into systems medicine does not give direct ways to analyse biological aspects of gendered experiences or enable critical reading of how gender is implemented in molecular medicine. Instead, by investigating why gender

[22] Keller 2005, 5.
[23] See for example Happe 2006, 190; Lock 2011, 236.
[24] See Weasel 2016.
[25] See Richardson 2015.

differences are not acknowledged in the current systems medicine research at institutes such as FIMM, it is possible to further consider what it would require to study gendered differences in molecular medicine research. As underlined before, gender then is not a given category but a question mark that can help to scrutinise the possibilities of bringing systems approaches to broader social healthcare practices as gender differences remains an active question highlighted by gender medicine.

I argue that it is not only possible to undertake a feminist analysis of systems medicine research but such analysis can help to outline fruitful ways of collaboration between social sciences and life sciences. My research contributes to current feminist research by further considering the potentialities that systems biology approach has when applied to medical research practices. While feminist researchers have emphasised systems approaches as something which underline the complexity, openness and dynamics of biological organisms it is important to ask, in addition, what happens when such an understanding is applied to medical research and practices that have practical aims of effectively preventing diseases and treating individual patients. I maintain gender medicine's claim that personalised medicine initiatives do not erase the need to consider gender as a factor in disease prevention and treatment. However, rather than juxtaposing the two as opposites, I wish to investigate their common basis and the benefits of gender approach for systems medicine. Thus seen, molecular medicine research gives ample possibilities for feminist engagement, even if gender differences are not in focus in the research, because it forces feminist scholars to actively ask what benefits a feminist approach could bring to molecular medicine research and *vice versa*.

The aim of my dissertation is to consider what it would mean to form a feminist engagement with systems medicine. To accomplish this goal, I will examine both the ways in which systems medicine research is currently organised as well as its connection to broader changes envision in personalised medicine literature. I will question how gender is currently

discussed in molecular medicine research. Why gender differences are not studied in systems medicine research? By comparing systems medicine approaches to gender medicine approaches, I will ask how gender approaches could benefit systems medicine research. Moreover, I will consider what it would require to include gender analysis into the research? Finally, I will consider the broader changes imagined to follow a personalised approach in medical care to further question how gender medicine approach differs from personalised medicine initiatives.

My answers to these questions are based on the fieldwork I conducted at FIMM. During my fieldwork, I interviewed FIMM's systems medicine researchers and other personnel working in systems medicine research projects. I observed researchers in their work and attended group meetings to gain a sense of the daily practices involved in systems medicine research. I also interviewed some of the researchers form the institute's other specialisation, human genomics, to gain a sense of differences in approaches in molecular medicine research. While I also rely on secondary literature to explain the broader changes envisioned in personalised medicine and gender medicine initiatives, my fieldwork at FIMM offers the foundation for my argument of the relevance to form a feminist engagement with systems medicine research, as also FIMM's researchers emphasised the potential relevance of gendered analysis to their future research.

Feminist engagement with systems medicine can offer a fruitful basis to address the changes taking place in life sciences. I argue that it is necessary for feminist scholars to move beyond considering systems biology as an inspiration to examining how its implementation to medical field can change the ways in which national healthcare is organised. As I explain in Chapter 1, with the help of Helen Longino's list of feminist virtues, a feminist engagement with life sciences should aim to contextualise research practices in order to consider their broader social implications. The concept of gender is useful when framing this investigation. In Chapter

2, the concept of gender functions as an analytical tool helping to understand the differences between human genomics and systems medicine research at FIMM. At first sight, the difference in relation to gender is striking: gender is always acknowledged in clinical population statistics analysed in human genomics whereas in systems medicine the focus is on explaining biological mechanisms of cancer and, thus, gender differences are not included in the analysis. However, a deeper look into FIMM's research shows that while gender is included into human genomics research, this remains at the level of acknowledging possible gender differences in the data but not further studying their basis. In systems medicine, on the other hand, gender differences are present when thinking how to bring molecular-level information into clinical treatment as they need to account of gender differences in treatment outcomes.

While my theoretical focus is on the question of gender in systems medicine research, I do not limit my description of FIMM's research only to the instances in which gender was mentioned but, rather, dedicate pages to elaborate how systems medicine research at FIMM is practiced in different ways (Chapter 3). A central challenge, when considering the possibilities to apply systems biology approaches to medical research, is to address patient variation in the research. As this variation includes also gender differences, a focus on gender could benefit systems medicine research. Thus, it is essential to question to what extent the current research practices at FIMM fit into the descriptions of personalised medicine as described in the literature and, secondly, how the study of gender differences could be seen in relation to these images for the future of systems medicine (Chapter 4). I will argue that the difference between gender medicine and personalised medicine is not so much that they would focus on different things, but that personalised medicine initiatives rely on individual responsibility to monitor one's own health whereas the gender approach, highlighting both biological and social factors involved into disease emergence, also stresses the need to consider social inequalities when considering preventative measures. Therefore, gender medicine approaches could benefit

personalised medicine but a further discussion is needed about the development of broader healthcare strategies.

In the final chapter, I will consider how the analysis presented in previous chapters could help to form active feminist engagement with systems medicine research. I will juxtapose my analysis of current systems medicine research with recent feminist analyses on epigenetics to question how the engagement with life sciences has seen to benefit feminist theories. I will stress that this engagement is approached not only as a way to emphasise the interconnectedness of nature and culture in human biology but new approaches in life sciences are seen to benefit feminist politics as well. I will consider the benefits that a feminist approach can bring to systems medicine research and to healthcare planning. I will conclude the chapter by addressing the need for feminist scholars to consider broader social requirements needed for systems medicine research and the possible ethical and legal challenges in generating big data for medical research.

My analysis of systems medicine research contributes to feminist science studies by offering a further understanding of what kind of data is needed for gendered analysis, emphasising the difficulties in collecting standardised lifestyle data. Combined with the current emphasis on big data in medical research, this is a question that surpasses the need to just look into the values in research communities and funding bodies but requires more active discussion about who can gather, access and for what purposes analyse collected data. Therefore, to formulate feminist engagements with new biomedical approaches, feminist scholars need to understand the changing relations between science and society and be actively included in the discussion of not only what kind of research is needed but how better research could be organised. Thus, I argue, a feminist engagement with systems medicine needs to go beyond the research practices done in an institution such as FIMM, to consider the broader changes currently taking place in biomedical research and societal healthcare planning.

Chapter 1

Feminist Science Studies as the Theoretical and Methodological Basis for the Study

This chapter is divided into two parts. The first part outlines the theoretical basis for my study, explaining how my focus on systems medicine stems from feminist science studies and feminist new materialism. Moreover, in the first part, I will explain why the concept of gender is a useful analytical tool for engaging with systems medicine from a feminist standpoint. The second part explains the methodology I used when conducting my fieldwork at the Institute for Molecular Medicine Finland (FIMM). As my methodology is influenced by my readings on feminist science studies and new materialism, my aim in this chapter is also to show the ways in which the chapter's two parts are interlinked.

In Part One, I will show why systems medicine is of interest to feminist scholars. I will do this by considering the grounds for systems medicine from the perspectives of "feminist virtues", as listed by Helen Longino in her article "Gender, Politics, and the Theoretical Virtues," published in 1995. Moreover, I will link my study on systems medicine to the recent feminist new materialist scholarship, which highlights the need to examine matter as an active part of knowledge production. The focus on materiality in new materialism has arisen from the critique towards the sex/gender division in feminist studies, stating that the emphasis on gender/sex as social constructs has given the defining role to cultural deciphering of biological information, leaving matter itself passive in knowledge production. While I acknowledge the challenges posed to the "newness" of new materialism in feminist science studies, especially when considering the works of Donna Haraway from the 1970s and 80s,[26] I highlight the

[26] See Haraway 1988, 1989 and 1991.

importance of its emphasis to engage with science-in-making in order to grasp how scientists can apply the notion of complexity in biological research. My focus on FIMM's research also gives an apt possibility to consider the role of categories such as gender in molecular medicine research as systems medicine research at FIMM combines the treatment and study of individual patients to that of disease. I maintain that while systems medicine researchers at FIMM do not include gender in their molecular-level analysis, closer focus on their research activities and strategies can help to further question the role that sex/gender division has on molecular research and how it links to the idea of complexity in life sciences.

In Part Two, I will elaborate how my research methods, following Bruno Latour's Actor-Network Theory, have supported my aim to offer an analysis of systems medicine research and its connection to Finnish healthcare planning and medical research by using gender as an analytical tool. Part Two also includes general information about FIMM to clarify the basis of my analysis in the following chapters.

Part I

Feminist Science Studies, New Materialism and Sex/Gender in Molecular Medicine Research

My work rests upon, and has been shaped by, feminist science studies. One of the strengths and challenges of this area of study is that it contains within it a heterogeneous group of scholarly works, ranging from examining gender relations in scientific work to using gendered analysis when pointing out epistemological shortcomings in scientific research. This heterogeneity makes it difficult, if not impossible, to define feminist science studies as a field, as noted by

scholars attempting such a task.[27] Still, since the late 1970s these studies have pointed out the rationale for centralising a gendered focus in science studies that can benefit natural scientists as well as historians, philosophers and sociologists of science. These studies have influenced my own work not only by offering theoretical tools to shape and sharpen my research and analysis but also by offering me a clear sense of the need for gender studies scholars to engage with natural science research and researchers. The need for an active engagement with life sciences has also been emphasised by new materialist scholars, wishing that this would help bring questions about materiality closer to feminist theories. In this part, I will offer a more elaborate description of both feminist science studies and new materialism together with a consideration of why a focus on systems medicine is interesting for feminist scholars. Furthermore, I will show why gender is a useful analytical tool when examining systems medicine despite the fact that systems medicine researchers at FIMM did not use this category in their daily work.

1. Feminist Science Studies

Feminist science studies as a field started at the beginning of the 1980s when feminist scientists began to raise awareness of sexism and androcentrism in science. Some scholars examined gender in scientific work, focusing on the contributions of female scientists and institutional sexism.[28] Others, on the other hand, used gendered analysis to point out epistemological issues in scientific research. My research focuses on the latter approach, examining how gendered

[27] See for example Subramaniam 2009 and Grebowicz & Merrick 2013.
[28] See for example Rossiter 1982 and 1995, Harding 1986 and Rosser 2004. For some scholars, such as Harding, there exists a strong link between highlighting institutional sexism and epistemological problems in science as her theory of strong objectivity maintains that unprivileged subjects' involvement in scientific research can make it more epistemologically sound.

differences are acknowledged and taken into consideration in the research design in molecular medicine research.

While describing feminist science studies as a field is challenging, its foundation is based on the studies highlighting social aspects of scientific research. To understand the multiple ways in which social and historical context can affect scientific research, it is necessary to view, borrowing Michel Foucault's words, "the politics of scientific statement". As Foucault states these politics are "not so much a matter of knowing what external power imposes itself on science, as of what effects of power circulate among scientific statements, what constitutes, as it were, their internal régime of power, and how and why at certain moments that régime undergoes a global modification."[29] One of the pivotal works to insist on the importance for such an analysis is Thomas Kuhn's book *The Structure of Scientific Revolutions*, published in 1962, where he questions the positivist ideal of cumulative and self-correcting rational science by pointing out how "normal science" does not aim to challenge but rather to support accepted scientific paradigms.[30] In practice, this means that certain information is "black boxed" in scientific research, leaving its basis unquestioned.[31] In other words, research rarely starts from scratch but usually rests upon broader frameworks and methodologies, accepted and maintained by the most of the scientific community. Kuhn's book is now considered as a classic work in the study of sociology of scientific knowledge and it has inspired research on the social aspects of scientific knowledge production. As Janet Kourany notes, the importance of Kuhn's work was in its insistence that philosophy of science, which had been centred around the logic of scientific knowledge claims, needed to consider how these claims related to the historical and social context and the scientific practices that produced them.[32] Although feminist scholarship

[29] Foucault 1980, 112–113.
[30] Kuhn 1970, 10–11.
[31] Latour 1987, 2.
[32] Kourany 2010, 29. Kuhn was not the only philosopher of the time to criticise the scope of and focus of philosophy of science. Kourany notes that influential work on socialising and historicising philosophy of science was also

has approached scientific research from multiple directions, one of the main emphasis in feminist science studies has been to critically evaluate how scientific knowledge production is not only social but also gendered.

1.1. The Concept of Gender in Feminist Science Studies

The focus on gender as a critical concept widened the scope of feminist science studies, which initially focused largely on female scientists' work in natural sciences, to include philosophy, history and sociology of science. As noted by Evelyn Fox Keller and Helen Longino in the introduction of the book *Feminism and Science*, published in 1996, this "has raised important yet heretofore unasked questions about the content and practice of the natural sciences, about the forms of interaction with the rest of the natural world that scientists have historically cultivated, and about the goals that have traditionally been idealized in the natural sciences."[33] For example, Emily Martin's work questioned how gendered metaphors influenced the ways in which fertilisation was wrongly described by portraying egg as the passive and sperm as the active participant;[34] Donna Haraway's analysis of primatology showed how simian behaviour was explained through existing ideas of gendered relations, underlining reproduction as the guiding principle in primatology;[35] and Londa Schiebinger's historical studies noted how society's gender relations shaped the taxonomies in natural sciences, even the descriptions of plants.[36] These examples show the utility of gendered analysis in history, sociology, and philosophy of science.

Importantly, feminist science studies underscored that gender biases have resulted in less rigorous scientific research also in medical studies. Evelyn Fox Keller remarks that gender

done by Paul Feyrabend, Norwood Russel Hanson, Stephen Toulmin, Imre Lakatos, Ernan McMullin, and Dudley Shapere.

[33] Keller & Longino 1996, 2.
[34] Martin 1991.
[35] Haraway 1989.
[36] Schiebinger 1989 & 2006.

biases have directed research towards health questions from a male perspective, for example, by focusing on female rather than male contraceptives.[37] Recent scholarship has also highlighted that medical research often neglects to study gender differences in disease emergence and progression, which can influence the effectiveness of disease prevention and treatment. This has led into gender medicine initiatives within the medical community.[38] What is more, feminist researchers have noted that gene-focused methodological approaches in molecular medicine have limited the scope of research, making it possible to neglect possible gender related differences in basic research. Keller calls this the "master molecule" approach as it places research emphasis on entities such as genes and offers a hierarchical model of biological mechanism rather than examines the various interactions within cells.[39] Based on these historical and contemporary case studies, feminist science studies has been keen to show how gendered focus challenges the view of science as value free and, thus, has encouraged further discussion on what is meant by scientific objectivity.

1.2. Values in Scientific Research and their Feminist Alternatives

Feminist scholars have argued that feminist science studies can function as the basis for thinking how to make scientific research more inclusive and rigorous. Best known of these suggestions are feminist standpoint epistemology, Donna Haraway's situated knowledges, and Helen Longino's science as social knowledge.

Feminist standpoint epistemology is based on the idea that scientific research would benefit from a more active incorporation of feminist values. One of the approaches, known especially through Sandra Harding's notion of "strong objectivity", is to identify women as better equipped to initiate critical values in scientific research as "[t]hey have less to lose by

[37] Keller 1996, 29–30.
[38] See for example Schiebinger & Schraudner 2011 and Baggio et al. 2013.
[39] Keller 1996, 38.

distancing themselves from the social order; thus, the perspective from their lives can more easily generate fresh and critical analyses."[40] Harding's latest book *Objectivity & Diversity* (2015) continues to argue for the need to take an active stance against the view of science as value free but, in this work, the emphasis is less on womanhood as a basis of resistance but rather on the need to incorporate participants from diverse cultural, social and geographical locations to scientific research. Their viewpoints, Harding maintains, will benefit discussions of research's social benefits and responsibilities.[41] Similar notions of the value of having underprivileged subjects present in scientific work and decision making is noted by Donna Haraway in her article "Situated Knowledges" (1988). Her emphasis is on the need for science studies to always look closely into the practices that produce particular scientific knowledge, rather than imagine a universal basis for scientific research. She argues that scientific research would be more rigorous and conducted more fairly if it would embrace multiple differing viewpoints.[42]

Another approach in feminist standpoint epistemology has highlighted feminist values, rather than womanhood or other subject categories, as the basis for forming an alternative for a value free science.[43] A central question in this approach has been how to make sure that feminist values, then, would not reproduce biased research?[44] An additional problem with this approach is that it leaves open the question of what are "feminist values" based on? This issue has been noted by Helen Longino in her 1995 article "Gender, Politics, and the Theoretical Virtues," where she considers what would be required from scientific research for it not to fall into gendered biases highlighted by the feminist critiques of science of the time. Longino's own approach to values in science highlights the need for a transformative criticism within the

[40] Harding 1991, 126.
[41] Harding 2015.
[42] Haraway 1988.
[43] See, for example Anderson 1995.
[44] See, for example, Anderson 2004.

scientific community. In other words, science could include value based research as the scientific community can actively ensure that the research is also conducted in a proper scientific manner, for example, through peer review.[45] Kourany, however, notes that this framework would leave the scientific community itself free of scrutiny and, thus, enables a possibility that those who bring in needed critical observations would become unable to enter scientific communities or their values would not be supported.[46] Still, the importance of Longino's work, elaborated in her 1995 article, is that it requires a deeper examination of what constitutes a feminist value that should be supported to benefit research.

In her 1995 article, Longino creates a list of "feminist virtues" with which it would be possible to examine how well a certain scientific research answers to feminist concerns arising from gender biases both in organisation of scientific research and in ontological assumptions guiding scientific methods. This list is formed in contrast to values listed by Thomas Kuhn, viewed as "traditional values" in scientific research. The list, as presented in her article,[47] goes as follows,

Feminist list	*Traditional list*
Empirical adequacy	Accuracy
Novelty	Internal /External Consistency
Ontological heterogeneity	Simplicity
Complexity of interactions	Breadth of scope
Applicability to human needs	
Diffusion of power	Fruitfulness

It is important to note that Longino does not set this list as a foundational list of *values*, as could be said in regards to the traditional list, but as feminist *virtues* that stem from the feminist critiques of the time. This means that fulfilment of these requirements does not automatically mean that science would be perfect but "one must look instead at the grounds that are offered

[45] See Longino 1990.
[46] Kourany 2010, 58–62.
[47] Longino 1995, 392.

for treating them as virtues and the ways in which their deployment in particular scientific arguments and research programs resonates with conditions in the social and political context of the research."[48] In other words, looking at scientific practices through this list of virtues can help to consider whether scientific research is, on the one hand, avoiding feminist critiques against (previous) scientific practices but, on the other hand, this assessment should be done in accordance to the social and political context in which the research is made. Hence, Longino's framework helps to explain why systems medicine should be seen with interest by feminist scholars but also why, as I argue, it is necessary to examine how systems medicine research operates in practice.

2. Systems Medicine Through Feminist Virtues

Systems medicine approaches have emerged from a similar critique toward reductionism in scientific research that was highlighted by feminist scholars, such as Evelyn Fox Keller, during the time when Longino's piece was written. At the end of the 20th century, many scientists, as well as popular science literature, envisioned a future where scientists would be able to understand and control biological phenomena as their genetic foundation would become clearer. This hype about the future of genetic research culminated in the Human Genome Project (HGP) which resulted in sequencing the whole human genome in 2001.[49] However, HGP surprised many by revealing that the number of genes in humans was less than anticipated, leading to a conclusion that genetic diversity was caused by complex genome-wide interactions. Thus, biologist and historian of science Hans-Jörg Rheinberger states "today it seems more appropriate and may ultimately even prove sufficient to speak of genomes or simply 'genetic

[48] Ibid., 396.
[49] For an account of genetic research in the 20th century, see Keller 2000.

material' rather than genes, whether it is a question of organismic function, development, or evolution."[50]

Systems biology research, which is the basis for systems medicine, is one outcome of this organism-based view that aims to account for the complexity in biological research. Recent feminist scholarship has considered systems biology as a potentially beneficial starting point for feminist scholars to engage with natural sciences as it challenges genetic reductionism.[51] Longino notes, however, that criticism towards reductionism in scientific research is not necessarily connected to feminist criticism. This is the case, for example, in Richard Lewontin's critique towards genetic reductionism.[52] Therefore it is noteworthy to question how systems medicine relates to the feminist virtues highlighted by Longino. To better illustrate how systems medicine research challenges genetic reductionism and the "master molecule" approach that Keller criticises, and why, in broader terms, systems medicine research should be studies from gendered viewpoint, I will look at it through Longino's list of feminist virtues, starting with the question of novelty.

2.1. Novelty

Longino considers novelty, as opposite to Kuhnian internal/external consistency, as a feminist virtue in scientific research. She defines novelty as "models or theories that differ in significant ways from presently accepted theories."[53] Longino sees this as a virtue given that science's theoretical frameworks in the 1990s "have functioned—directly or indirectly—in gender oppression."[54] The novelty of systems medicine research is based on its foundation in systems biology. As Sara Green points out in the introduction of the book *Philosophy of Systems Biology*

[50] Rheinberger 2010, 165. For examples of such accounts see Lewontin 2002 and Oyama 2000 who are seen as representatives of 'developmental systems theory'.
[51] See, for example, Coole and Frost 2010, 15–18.
[52] Longino 1995, footnote 5.
[53] Longino 1995, 386.
[54] Ibid., 392.

(2017), "systems biology is often defined in opposition to reductionist methodologies."[55] This is because it aims to tackle the challenges posed to research by the complexity of biological organisms.

As Keller points out, biological research has long been based on the experimental study of organisms and went against the formation of larger theories that would explain biological functions. Keller states that such an approach differentiates biology from physics, where theory and experiments have more easily fused together in the fields such as quantum physics.[56] The implications of separating theory and practice in biological research can also be seen in the discussion about "gene talk" in science: rather than offering a larger theory to explain genetics, biology has used the concept of the gene as a tool that has been adapted to different experimental conditions.[57] This particularity of biological research could be seen as one reason why biomedical discourse, both within and outside scientific research, glorified the concept of the gene in scientific explanations. This history of biological research can be seen to culminate in the hype towards HGP as a way to decipher human biology.[58]

Increasing understanding of how the functions of genes were dependent on complex interactions within the cell, however, has shifted the focus of biological sciences into mapping genomic-wide relations. This change is often termed as a turn from genomics to "postgenomics".[59] The change in research focus was made possible by new computing technologies. What has changed in recent years, then, is the way in which biological research co-operates with researchers from the fields of engineering, computer science, physics and mathematics in an attempt to map out complex biological systems. As Leroy Hood, founder of the Systems Biology Institute in Seattle, states: "systems biology simultaneously studies the

[55] Green 2017, 4.
[56] Keller 2002, 1–3.
[57] See Rheinberger 1997 and 2010.
[58] Keller's book *The Century of the Gene* (2000) offers a more elaborated account of the "gene talk" both within and outside science.
[59] See Richardson & Stevens 2015 and Rheinberger & Müller-Wille 2017.

complex interaction of many levels of biological information—genomic, DNA, mRNA, proteins, functional proteins, informational pathways and informational networks—to understand how they work together."[60] Keller states that "the net effect [of this co-operation] is the beginning of an entirely new culture that is at once theoretical and experimental."[61] As a possible implication of systems biology, Keller sees a change not only in the practices of biological sciences but also the potentiality to alter scientific vocabulary. Keller describes this wish of the change in scientific lexicon by stating "for too long we have tried to build a biology out of nouns, a science constructed around entities. Perhaps it is time for a biology built out of verbs, a science constructed around processes."[62] It is undoubtedly the case, then, that systems biology can be viewed as a novel approach in natural sciences. Moreover, relevant when considering its link to Longino's feminist virtues, is to see how this novelty is based on the attempt to account for the ontological heterogeneity of biological organisms.

2.2. Ontological Heterogeneity

As Longino notes, a theoretical framework is always based on a certain kind of ontological view that "characterizes what is to count as a real entity in its domain."[63] She sees ontological heterogeneity as a virtue because it would give equal standing to different kinds of entities in scientific explanations. This, she states, should be seen as a virtue because it values individual differences and, hence, differences are perceived more as a resource than hindrance to research.

As a feminist example of research that takes ontological heterogeneity into account, Longino uses Barbara McClintock's studies on maize cytogenetics (study of structure and functions of cells), as described by Keller.[64] McClintock challenged the hierarchically

[60] Hood cited in Keller 2005, 5.
[61] Ibid., 7.
[62] Ibid., 9.
[63] Longino 1995, 387.
[64] See Keller 1983.

structured view of molecular entities by suggesting a more interactionist approach in understanding the functions within cells. This led to the formation of some of the basic principles of gene functions and she was awarded a Nobel prize in physiology the same year as her biography, written by Keller, was published. The reason why Longino highlights McClintock's approach in her work is because it is a better description of the functions of the cell. In other words, according to Longino, McClintock's work can be seen as feminist as it went against the mainstream molecular research methodologies, based on hierarchical descriptions of the cell structure, in order to more precisely describe what she observed in maize cells. Ontological heterogeneity, understood in this way, becomes a feminist virtue as it can describe the world more accurately. In systems biology research, the aim to account for ontological heterogeneity in biological organisms has resulted in a new kind of approach to studying biological organisms.

Olaf Wolkenhauer and Allan Muir point out that complexity related to cell-biological systems arises both from the complexity of the inherent nature of the cell and from the methodological challenges this posits for research.[65] What, according to them, separates systems biology from previous research is that,

> [w]hile investigations into the *structural (material) organization* of molecules and cells have dominated molecular and cell biology to this day, with the emergence of systems biology there is a shift of focus towards an understanding of the *functional organization* of cells and cell populations, i.e., the processes ("laws" and "mechanism") that determine the cell's or organ's behavior.[66]

Wolkenhauer and Muir point out that systems theory posits the need to consider both the cell's interior (how the components within a cell interact when bringing together a cell's structure and function?) and exterior (how different cells interact when maintaining a higher level of structure and function?) aspects. What is central to understanding the ontological stance related to systems biology is that these processes form an *organized complexity*; meaning that

[65] Wolkenhauer & Muir 2011, 355.
[66] Ibid.

it is possible to consider potential laws and designs that govern these processes. Complexity, then, is connected to the fact that while it is possible to consider how different parts are related to one another, their relation is dynamic, and as such, not reducible to its parts. In tackling this complexity, Wolkenhauer and Muir argue that we can consider three major processes: Metabolism of cells (processes that construct and maintain the cell), cell signalling (how cell function is dependent both from internal and external relations) and gene expression and regulation (how information from DNA is translated into gene products such as protein). Due to the complexity of networks related to all of these processes, research in such fields is often called "Omics" disciplines (such as "metabolomics") to highlight the dynamic nature of the studied phenomena.[67]

As Wolkenhauer's and Muir's work highlights, the challenge for systems biology research is how to successfully account for biological complexity. One perquisite for such a work is to establish an ontological basis and epistemological plan to map out functional organisation of cells and cell populations. On a more practical side, this brings forth a question of how researchers can account for the complexity of such interactions. This is also something that Longino sees as central for feminist approaches.

2.3. Complexity of Interactions

Complexity of interactions in Longino's list refers to theories which "treat relationships between entities and processes as mutual, rather than unidirectional, and as involving multiple rather than single factors."[68] The view of reciprocal interaction is connected to the virtue of ontological heterogeneity. It requires researchers to acknowledge that organisms constitute of multiple different kinds of entities which interact with their environment and can take part in

[67] Ibid., 366–368.
[68] Longino 1995, 388.

the emergence organism's state, such as diseases. This virtue, however, goes a step further in requiring that researchers not only acknowledge the complexity of interactions but actively include it into their research designs. In systems biology research, this has been taken into consideration, firstly, through an inclusion of mathematical and computational approaches into research methods. These technologies are used to map out complex interactions. Secondly, systems biology literature highlights the need for an active interdisciplinary collaboration because mapping out such interaction requires knowhow from researchers with different disciplinary backgrounds.

Philosopher of science, Miles MacLeod, notes that there are a variety of projects working under the label of systems biology, with different methods and research goals.[69] However, what he sees as a connective factor between different types of systems biology research is the "shared commitment to model complex biological systems using computational and mathematical resources."[70] Mathematical and computational advances are so important for the succession of systems biology because they enable researchers to study, in addition to small-scale systems via classical molecular biology methods, large-scale systems.[71] Furthermore, Wolkenhauer and Muir see the possibility to move from small to large-scale systems as central when considering possible laws and organisational principles that related to the functions of biological systems.[72]

However, it has been questioned to what extent systems biology methods can challenge explanations that focus only on certain biological mechanisms at a time. As Wolkenhauer and Muir point out, omics disciplines posit a great challenge for research methods since "to model inter and intracellular processes one requires quantitative spatiotemporal data for a relatively large number of components. At present these are not available, forcing us to handle uncertainty

[69] MacLeod 2015, 85.
[70] Ibid.
[71] Ibid., 86.
[72] Wolkenhauer & Muir 2011, 362.

and "reduce" complexity."[73] MacLeod remarks that this usually leads researchers to conduct their experiments in classical frameworks of either bottom-up (which aims to build a model system-level by connecting data gained from experiments) or top-down (which aims to model the structure of large-scale systems by "reverse engineering" the data gained from high-throughput data). However, he states that systems biology researchers "assemble information from different contexts and employ computational methodologies to infer structures when necessary".[74] Thus, systems biology functions in-between micro and macro levels of modelling.

MacLeod highlights that this should first and foremost be considered as a research strategy that can help the researchers to break down the complexity of the studied systems and thus aid the planning of further models.[75] Rather than seeing this as a failure of researchers to handle complexity, MacLeod describes this as an internal part of systems biology, since he (at least before the establishment of the field) connects this with the engineering quality involved in systems biology research. For him integrating different sources of information together is not just a matter of how to combine the sources but it is a process, which "importantly is a process of looking up, down and around."[76] This process for him is an essential part of systems biology, since the practicalities of the research necessarily force researchers to search for mechanistic explanations. However, he argues, "if philosophers focus on mechanistic explanations they miss the creativity of these epistemic strategies and the innovative ways systems biologists can develop their goals to achieve mathematical tractability with extremely challenging problems."[77] To stress the point, for him the mesoscopic modelling (that balances between top-down and bottom-up approaches) is not a sign of methodological failure but a sign that researchers are fully aware how their models are in-between two ends, which not only keeps

[73] Wolkenhauer & Muir 2011, 368.
[74] MacLeod 2015, 87.
[75] Ibid.
[76] Ibid., 89.
[77] Ibid., 99.

them on their toes but also makes them consider how to develop the model accordingly. This combination of different modeling levels requires an active interdisciplinary collaboration.

MacLeod states that if one wishes to understand systems biology, it is important to consider how systems approaches to biology require different scientific disciplines to co-operate.[78] As noted by Green, "[s]ystems biology combines traditional biological research strategies with methodological and theoretical frameworks from various disciplines including physics, engineering, computer science, and mathematics."[79] In order to understand how this collaboration supports the modelling practices described by MacLeod, it is important to view this collaboration in an interdisciplinary manner rather than a multidisciplinary one. In an interdisciplinary study, researchers from different fields work together on a set of questions rather than just combine their independent studies.[80] As philosopher Marta Bertolaso notes when discussing the strength of systems approaches,

> The interdisciplinarity I am talking about is thus not just the sum of disciplines, it is not enough to find a common language and methodology, but implies sharing a common objective that drives a focused research. Cooperation is more than aggregation and its output is not to hold the capacities of the component parts; it depends on the dynamic properties of the network and, then, its capability to generate new ideas that were not there before. Like in an organism, parts, once entangled in a unity, perform new activities and behavior. Systemic perspective thus allows recovering a new perspective any time it is required, listening to different disciplines and looking back to the already done research.[81]

Following Bertolaso's thinking, the interdisciplinary approach in systems biology is beneficial because it keeps them alert to countless possibilities—"*recovering a new perspective any time it is required."*

Based on the ontological and epistemic changes that systems approaches have brought to biological research, it is fair to say that systems biology research fulfils Longino's feminist virtue requiring the researchers to include complexity of interactions to their study designs as

[78] Ibid., 95.
[79] Green 2017, 1–2.
[80] On the distinction between interdisciplinary and multidisciplinary, see Huutoniemi et al. 2010.
[81] Bertolaso 2011, 247.

this complexity is the starting point of systems approaches. It is important to note, however, that thus far my explanation of why I see systems medicine research as interesting for feminist scholars is its foundation in systems biology. As such, systems medicine is of interest for feminist scholars due to its foundation in an approach that challenges prior genetic reductionism. In feminist new materialism, systems biology has already been greeted as a new way to approach biological entities in an interesting manner.[82] Yet, what makes systems medicine even more interesting for feminist scholars, in my view, is its connection to medical practices. This is because systems medicine allows scholars to examine how systems approaches are applied into practical clinical questions. As systems medicine research programs, in institutions such as FIMM, aim to treat individual patients while gathering more precise information about diseases, they are suitable sources to question the extent to which researchers can apply a systems approach in medical research. This way, systems medicine research can also be analysed through Longino's fourth virtue, which questions how research projects relate to social needs and inequalities.

2.4. Applicability to Human Needs and Diffusion of Power

The fourth feminist virtue highlighted by Longino is scientific studies' applicability to human needs and the way in which different people have access to participate in the research and how it benefits them. Longino sees these as virtues because they set a pragmatic goal for research. It can, then, be asked to which extent the scientific theories and practices "improve living conditions in a way that reduces inequalities of power."[83]

Systems medicine is a practical application of systems biology. Since the start of systems medicine programs from the beginning of the 21st century, their relevance for medical research

[82] See Coole and Frost 2010, 15–18.
[83] Longino 1995, 394.

has gained ground. As Green notes "[S]ystems biology is expected to play a central part in future medicine, and projects under the labels of systems medicine, personalized medicine, P4 medicine and precision medicine indicate the directions we can expect medicine to follow."[84] The terms systems medicine, personalised medicine, P4 medicine and precision medicine are all used to indicate the need to establish a new kind of relation between molecular-level research and clinical treatment. By considering molecular differences between individuals, the proponents of personalised medicine argue, it is possible to create better treatment options for patients and individualise disease prevention strategies in the future. This would also enhance the role of individuals in creating disease strategies.

The four Ps under the name "P4 medicine" indicate the extent of the changes envisioned for medical research that applies systems approaches. The four Ps stand for predictive, preventive, personalised, and participatory medicine.[85] To put it simply, these four Ps suggest a need for a kind of healthcare that could take into account an individual's disease risks in order to prevent it from occurring and, when disease occurs, use molecular-level information to plan a more precise treatment that would be as effective as possible with as little harmful side effects as possible. The P standing for participatory indicates, in addition, that such plans require more than just changes in researchers' and clinicians' work. As Hood and Tian note in their introductory article to systems approaches in medicine, "patient-driven social networks for disease and wellness will be a driving force in P4 medicine. Society must access patient data and make it available to biologists for pioneering predictive medicine of the future."[86] This would mean an integration of big data approaches to medical research aiming to collect large-scale data sets to better comprehend individual differences in diseases and their emergence.

[84] Green 2017, 16.
[85] See Hood & Tian 2012.
[86] Ibid., 184.

This collected data could then be used to make more precise disease risk calculations to prevent diseases from occurring.

Taken together, these four Ps propose a new approach to healthcare, which would be more strongly devoted to the promotion and maintenance of wellness. One could argue that they follow the increasing emphasis in sciences to consider individuals' active participation in the production and application of medical research.[87] However, as Helga Nowotny states, a bigger change imagined to follow the big data approach in healthcare is to use computational force in calculation of disease risks that, then, function as the basis of prevention and treatment plans. This image goes as far as to consider a world where big data "no longer needs the judgement of experts and has dispensed with the question of asking *why*."[88] The rationale and possibilities to establish such healthcare practices has been, however, been questioned by recent research.

Annamaria Carusi has pointed out how the possibility to use big data, which is seen as an essential part of systems medicine research, introduces new ethical and social questions about gathering, making available, and using personal health data in research. These questions surpass the technical questions related to data protection and anonymity as systems medicine research needs communities' support for gathering and using personal health data.[89] Such discussions are present, for example, in the formulation of biobank legislation when considering what kind of information can be collected and who has access to it.[90] As Helga Nowotny reminds, personalised medicine is still in "its infancy" and has to face these kinds of challenges in order to operate effectively.[91]

[87] The increased individual participation in forming scientific research and its new directions has been discussed also in Nowotny, Scott & Gibbons 2001, Nowotny & Testa 2010, and Rose 2007.
[88] Nowotny 2016, 56. For the changes in healthcare connected to personalised medicine, see also: Langkafel 2015 and Pavelić et al. 2016
[89] See Carusi 2016 & 2017.
[90] See, for example, Fobelets & Herman 2009 and Lenk et al. 2011.
[91] Nowotny 2016, 97.

Going beyond the acquisition of biological data, scholars have also raised doubt whether P4 medicine offers the holistic and precise approach to medicine often associated with it. Concerns have been raised about the potential risk for over diagnosis and insufficient decision making with the increased aims in computation-based disease prevention.[92] These concerns are based on a defining question of what is meant by the holistic approach linked with systems medicine. Henrik Vogt, Bjørn Hofmann, and Linn Getz argue that rather than stemming from the idea of holism as seen in humanistic tradition, systems medicine research as envisioned in the current literature suggests a more *technoscientific holism* approach in which "each person's life process is defined in biomedical, technoscientific terms as quantifiable and controllable".[93] In addition to possible clinical misdiagnoses, they see that technoscientific holism contains within it a danger as "[b]iomedicalization may distort our understanding of problems that should be understood on the personal, social and political levels by describing them in reductive biological terms."[94] Thus, even if systems medicine aims to account for complexity of biological organisms, there still remains a question to what extent these approaches consider health together with the question of what constitutes a good life, as is the case of holism in the humanistic medical tradition.[95] In other words, to what extent can systems medicine research account for the complexity of health and wellbeing?

It should be noted, however, that the analysis made by Vogt, Hofmann, and Getz is based on literature advocating for personalised medicine, much of which is written by Leroy Hood, who has been active in emphasising the need for the systems medicine approach in medical research and healthcare organisation. It remains a question, then, to what the extent does the current systems medicine research fill these ambitions and what forms systems approaches have taken in medical research. My research aims to offer a better account of both systems medicine

[92] Green & Vogt 2016, Fischer et al. 2016.
[93] Vogt et al. 2016, 307.
[94] Ibid., 320.
[95] Ibid.

research, based on my fieldwork at FIMM, considering what it means in practice and how it relates to the broader aims associated with personalised medicine. As noted in the methods section in Part Two of this chapter, my fieldwork was based on an aim to learn how researchers defined the scope and aim of their own research. Although most of the systems medicine researchers at FIMM did not consider gender differences in their research designs, I maintain that one beneficial way to examine the extent to which current molecular research practices can incorporate biological complexities—especially when questioning environmental or lifestyle aspects—into the research is by asking what is the role of gender in molecular medicine's research designs. The last virtue in Longino's list helps to explain why the concept of gender is a useful tool in my analysis.

2.5. Empirical Adequacy

The final virtue in Longino's feminist list, empirical adequacy, addresses the feminist critique of scientific research focusing on sex-based biological differences. For example, Anne Fausto-Sterling's work has questioned the ways in which human behaviour has been explained to follow assumed sex difference and reproductive goals.[96] Instead, Fausto-Sterling has argued that an accurate study of sex difference would challenge binary sex division and, rather, talk about five sexes.[97] Longino argues that studies assuming dichotomous sex difference based on reproduction rest on poorly done standards of empirical adequacy. The requirement for empirical adequacy, according to Longino, means "agreement of the observational claims of a theory or model with observational and experimental data, present, retrospective, or predictive."[98]

[96] Fausto-Sterling 1997.
[97] Fausto-Sterling 1993.
[98] Longino 1995, 386.

However, Longino is careful not to insist on a certain way to conduct gendered analysis in biological research but, rather, emphasises the need for the scientists to consider what kind of information is needed to fully account for their research questions and aims. This is why Longino places this virtue against the seemingly similar Kuhnian value of accuracy. She emphasises their difference by noting how scientific research can be very accurate while simultaneously separating the studied object from its environment. As she notes, "[w]hen we detach a factor from the contexts in which it naturally occurs, we are hoping to achieve understanding of that factor's precise contribution to some process. But by taking it out of its natural context we deprive ourselves of understanding how its operation is affected by factors in the context from which it has been removed."[99] While Longino's urge towards empirical adequacy rose from the need to critique the assumed binary sex difference, her emphasis on the purpose of the research helps to understand how, in other research settings, demanding acknowledgment of gender differences is also a demand for empirical adequacy.

To consider how gendered analysis could be included into molecular research, I turn to recent literature in gender medicine. As the proponents of gender medicine argue, attention towards biological and social differences between genders is needed to form empirical adequacy in medical research. As noted by Londa Schiebinger and Martina Schaudner, there are notable gendered differences, for example, in the treatment requirement of cardiovascular disease that currently benefits males, in detection of osteoporosis that benefits females and a need to consider differences between XX and XY stem cells.[100] Thus, gender medicine initiatives within scientific communities have argued that medical research, including the research on a molecular level, should better account for gendered differences in disease prevention and treatment.[101] Gender differences discussed in gender medicine literature include

[99] Ibid., 395.
[100] See Schiebinger and Schraudner 2011, 162–163.
[101] See, for example, the statement plan of the International Society for Gender Medicine: <http://www.isogem.com/> [Accessed June 10, 2017]

both biological sex differences and differences influenced by social gender roles. In this characterisation, there is a distinction between biological sex, which is connected to sex hormones, and gender, which is connected to nutrition and lifestyle influenced by society, though researchers stress that such distinction also notes that sex and gender are closely interrelated in medical research.[102]

Gender medicine initiatives, that have largely stemmed from within the medical community, give a good basis to argue for the need to consider gender differences in medical research. Interestingly, the proponents of gender medicine also emphasise that personalised medicine does not take away the need to study gender differences in diseases as "large databases reveal that gender remains an independent risk factor after age, comorbidities, lifestyle factors, and ethnicity have been taken into account."[103] Hence, in my analysis, I have juxtaposed the molecular medicine research done at FIMM with gender medicine literature to better understand the ways in which FIMM's researchers talk about the relevance of studying gender differences in their own work.

After going through Longino's list of feminist virtues and systems medicine's relation to them, it is clear that systems medicine should be of interest for feminist scholars. While the systems biology approach has already been welcomed in feminist new materialist scholarship as it aims to account for biological complexity, systems medicine—possibly due to its newness—has received less attention in feminist research. As emphasised in relation to the last two feminist virtues, critical studies addressing personalised medicine question its possibilities to address the complexities of human lives. Gender medicine, on the other hand, sees gender as a concept challenging personalised medicine's emphasis on biological parameters. To what extent these criticisms reflect the current state of systems medicine research, and its link to broader healthcare planning, is a question addressed in the following chapters. Before that, it is

[102] See for example Regitz-Zagrosek & Seeland 2012, 5.
[103] Regitz-Zagrosek 2012, 4.

still important to consider how my research, then, sees the connection between engaging with systems medicine and acquiring a perspective that could benefit feminist engagement with life sciences. To elaborate this point, I will first explain how my work draws from feminist new materialist scholarship.

3. Feminist New Materialism and Engagement with Science-in-Making

My work is closely linked with feminist new materialism, firstly, because it made me interested in reading into systems biology literature and, then, question how the systems biology approach is applied in medical research. Secondly, new materialists underline the need to "engage with" natural sciences to grasp how scientific knowledge production is connected to the world it aims to describe. The fact that the same terminology has been used in the title of this dissertation—a feminist *engagement with* systems medicine—emphasises the extent to which this work has been shaped in regards to feminist new materialist approaches. To clarify the ways in which my research relates to feminist new materialism, I will start by defining the terms and its "newness" in feminist theory.

3.1. Newness of Feminist New Materialism

As Diana Coole and Samantha Frost assert in the introduction to the book *New Materialism* (2010), the "cultural turn" in social sciences, of which social constructionist feminists are seen to be a part of, emphasised the role of language, discourse, culture, and values in the analysis of society. While the cultural turn had an important role in criticising the straightforward meanings given to biological entities and their entanglement with power relations in society, Coole and Frost state that this criticism left matter itself a passive part of meaning production. For new materialists, considering materiality does not only entail questioning how material

reality influences human societies.[104] Instead, they relate the "newness" of the new materialism to the acknowledgement that notions such as matter, nature, and reproduction are not only shaped by current research and technologies but these practices also use different conceptualisations of the nature of matter. For them, the examination of the role of materiality in society is, then, also an ontological inquiry.[105] Moreover, this ontological inquiry is entangled with a need to challenge the anthropocentricism of Western metaphysics, drawing from scholarly fields such as posthumanism, which has criticised the ways in which humanism is based on dichotomies such as human/animal, self/other, and normal/abnormal, and ecofeminism.[106]

The reason why my project has been influenced by new materialist scholarship is not so much because new materialism brings materiality to focus in research, but because of its approach to materiality. The question of how new materialism differs from previous feminist theories has been voiced in Noela Davis' article *New Materialism and Feminism's Anti-Biologism* (2009), which was a response to Sara Ahmed's article published a year before. Ahmed critiques new materialist feminists for approaching earlier feminist theory as "anti-biology" because this created too narrow a view of feminist scholarship—excluding, for example, feminist science studies or race studies that had also focused on biological bodies.[107] While agreeing with Ahmed that it is crucial not to reduce the complexities of previous scholarship, Davis elaborates how new materialism differs from previous feminist theories. Davis' response to Ahmed highlights that the critique of the new materialist feminists towards

[104] Coole & Frost 2010, 1–4. This is also the basis with which new materialists differentiate themselves from Marxist materialism, which still presents matter as inactive. See, for example, Frost 2011, 72–73.
[105] Coole & Frost 2010, 5–7. The focus on ontological questions ties many new materialists to contemporary philosophers that challenge the ways in which western metaphysics have prioritised epistemology over ontology. See, for example, Bennett 2010, Bogost 2012, Bryant 2011, Harman 2009 and 2010, and Latour 1993. These authors are usually connected with theoretical notions such as actor-network theory (Latour), speculative realism, and object-oriented ontology. Also, for many *A Thousand Plateaus* (1988) by Gilles Deleuze and Félix Guattari, and especially their notions of assemblages and becoming, functions as the philosophical basis for considering materiality and the discursive as entangled. See for example Braidotti 2002 and DeLanda 2006.
[106] For further reading on posthumanism, see Haraway 2008 and Wolfe 2010. For ecofeminism, see Heise 2008.
[107] Ahmed 2008.

previous scholarship should not be seen as criticism of the absence of the biological body in feminist theory but rather a critique of the ways in which biology has been approached.[108]

Davis explains this difference by giving an example of Lynda Birke's and Sandy Best's study on menstruation from 1980 that Ahmed uses as an example of a feminist connection with biology before new materialism. Davis argues that although Birke's and Best's work is deeply embedded in biological accounts of women's biology, they still base their explanation of unusual menstruation on a separation between nature and culture. Davis uses the following excerpt from Birke's and Best's work to support her point,

> The complex set of changes referred to as 'premenstrual tension' varies greatly from individual to individual, and often from cycle to cycle within the individual… furthermore, since it is also culturally variable, we find it absurd to attribute it simply to women's biology. If it were a direct consequence of our biology, we might expect it to be *more constant in form*.[109]

Davis argues that this excerpt exemplifies how Birke's and Best's work is different from the ones of new materialist feminists since "there is no investigation or speculation as to how the ideational (cultural effects) *can* become physical… no wondering about how these two different 'substances' can mix together in the body."[110] Following this argument, Davis concludes the example by pointing out "it is the manner of their engagement with biology and with the question of nature that is the target of [new materialist] critiques."[111]

While I understand the differentiation that Davis makes between new materialism and earlier scholarship in the example of Birke's and Best's work, I see this differentiation less in the works of Donna Haraway, whose work Ahmed also highlights. Haraway's work from the 1980's already highlights the need to engage both with the feminist critiques towards social embeddedness of scientific research as well as engage with the ways in which knowledge is

[108] Davis 2009, 70.
[109] Birke & Best, 1980: 269, note 52 cited in Davis 2009, 72. Davis' emphasis.
[110] Davis 2009, 72–73.
[111] Ibid., 73.

produced in particular scientific settings.[112] Marget Grebowicz and Helen Merrick have noted in their critical study of Haraway's work that it can be challenging to talk about Haraway's work in relation to feminist new materialism might be a result of the difficulty to situate her work in feminist scholarship as it balances between feminist critique and engagement with scientific research.[113] Moreover, Haraway's argument for the need to consider "naturecultures", a term highlighting scientific research as connected both to nature and culture, does not stem from Bruno Latour's work, which is used by many new materialist scholars. Rather, Grebowicz and Merrick note that Haraway and Latour share their view towards social studies of science, which "demand that we take seriously 'what the world is made of' (some of which is translated through/in science), while also interrogating how it is made, that is, scrutinizing how and why science comes to know what it knows."[114] Thus, Haraway's work challenges the 'newness' of new materialism but also further highlights the need for feminist scholars to engage with science-in-making.

While one could, then, disagree that the new materialist approach is fully new in feminist science studies, it is notable that one difference between them is the way in which feminist new materialism has been open towards recent approaches in natural sciences as a way to talk about naturecultures. Although feminist scholars have always found also interesting examples from natural sciences, such as Keller's work on Barbara McClintock's studies on maize cytogenetics, these have been exceptions from the norm and, as such, fuelled the arguments for the need of feminist approach to scientific research. This is the case, for example, with Longino's list of

[112] Haraway 1988.
[113] Grebowicz & Merrick 2013, 30–33. This could also be seen in Davis' comment on Haraway in her response to Ahmed. Davis remarks in a footnote (2009, 80) that while she is not discussing Haraway's work in her article, she argues that Haraway maintains a distinction between biological and social. Davis refers to Vicki Kirby's work (1997, 146–147) where Kirby argues for this dichotomy in Haraway's work. However, Kirby's analysis talks little of the question of *situated knowledges* in Haraways work, which conceptually aims to tackle the ways in which feminist understanding of social inequalities could be brought together with an understanding of biological realities. Thus, Haraway maintains the value of feminist epistemologies in scientific work whilst going against the view of scientific work as purely social construction. See Haraway 1988.
[114] Ibid., 33.

feminist virtues. As I have already highlighted, however, the feminist new materialist scholars have used examples of recent approaches in natural sciences, such as systems biology and epigenetics, to show how new research fields in natural sciences help to challenge prior ideas of the separation between nature and culture or the hierarchical structure of biological organisms.

In this, feminist new materialism echoes a larger trend in the social sciences. Over the last few years, a growing number of social science publications have argued for an active engagement with natural sciences. As Lisa Blackman states in her introduction to the *Body & Society* journal's special issue on *The New Biologies* (2016), interest has spiked in novel approaches in natural sciences that are more open to questioning how humans' social embeddedness influences their biology. Blackman calls this a trend in which concepts such as "biosocial", "biocultural" and "political biology" "are taken to signal something new about the current conjuncture and the opportunities for sociologists and others to become more open to the biological and life sciences."[115] Feminist scholarship has been especially interested in the study of epigenetics, which examines the ways in which environmental factors influence biological mechanisms that regulate DNA expression, which can even be transgenerational.[116] As was the case with Karen Barad's influential feminist analysis of quantum physics,[117] feminist theorists have adduced natural science research that has challenged the limits with which the engagement between natural sciences and feminist theory have been seen. To accomplish this, it has been necessary to engage with science-in-making.

[115] Blackman 2016, 5.
[116] See, for example, Keller 2010, Frost 2014, Davis 2014, Lock & Palsson 2016, Weasel 2016, and Richardson 2017.
[117] See Barad 2003 and 2007.

3.2. Engagement with Science-in-Making

As Myra Hird argues in her article *Feminist Engagement with Matter* (2009), one way to approach the entangled relation between materiality and culture is to engage with science-in-making.[118] Coole and Frost state that one source of inspiration for the development of new materialism has been the advancement of natural science in the twentieth-century. They argue that, for example, creations of the chaos and complexity theories in the field of quantum physics have inspired a demand for a new ontology of matter that would replace a vision of substantial material *being* with an image of transformative, fluid and open-ended material *becoming.*[119] Though Coole and Frost emphasise that ontological questions raised by natural science are not transferred as such to social science theories, scientific theories still "inform expert witnesses who contribute to relevant policy making, and they gradually transform the popular imaginary about our material world and its possibilities."[120]

The challenge that scientific areas such as quantum physics, epigenetics and systems biology are seen to present to a biological essentialism is based on their emphasis on fluidity, complexity and openness.[121] Feminist scholars such as Lynda Birke, Margaret Lock, and Kelly Happe have argued that new areas of biology, such as epigenetics, should be of interest for feminist scholars, since they challenge a simplistic equation between the social definition of bodies and biological research.[122] However, it is not only the contemporary biological research that has inspired feminist scholars to think about the entanglement between matter and culture. For example, Grosz has examined the works of Henri Bergson and Darwin and Elizabeth Wilson has studied Darwin's and Freud's early works.[123]

[118] Hird 2009, 331.
[119] Coole & Frost 2010, 10–11.
[120] Ibid., 5.
[121] Karen Barad has also argued that Niels Bohr's quantum physics challenge the distinction between epistemological and ontological. See Barad 2007. Following her work, many new materialist scholars talk about "onto-epistemology" when addressing natural science research.
[122] See Birke 2000, Happe 2006, Lock & Kaufert 2001, and Lock 2011.
[123] See Grosz 2004 and Wilson 2002 & 2004.

However, the inspiration that science can bring to feminist research in these accounts seems to be tied to the fact that nature challenges simplistic essentialist characterisations, thus, challenging any socially biased binary sex definition. For example, Wilson argues that what is noteworthy in Darwin's research for feminist studies is that it points out how scientific material "contains schemes and wonders that are of immense significance for feminist theories of subjectivity, embodiment, and sexed and gendered identities".[124] What is more, Wilson states, the Darwin example questions the idea that only culture can be the source of versatility and instead sees scientific research as a potential site for inspiration about the material multitude. Wilson urges feminist to engage with Darwin since in *The Origins of Species* "there is no pre-given identity of form or function to be found anywhere in nature (…) rather there is mutation, inconstancy and radical interconnectivity that produces the identities and differences we recognise as individuals and species."[125] Engaging with science, then, seems to be about pointing out how material complexities end up challenging too simplistic and socially influenced categorisations.

The emphasis on material complexity in new materialist research raises the question of feminism's need to consider how the sex/gender relation is analysed in scientific research. As Frost notes in her article "Re-considering the turn to biology in feminist theory" (2014), feminist scholars can draw appreciation towards biological complexity from scientific approaches, such as epigenetics, but there is no need to base gendered identification to such biological explanations.[126] However, as I argued in relation to Longino's feminist virtues, systems medicine should be seen of interest for feminist scholars as it helps to consider to what extent systems approaches have been applied to medical research. In this kind of analysis, it can be beneficial to consider how gender differences in diseases are acknowledged in molecular

[124] Wilson 2002, 284.
[125] Ibid.
[126] Frost 2014.

medicine research. However, is gender a proper analytical concept to discuss this implementation when systems medicine researchers at FIMM did not work with the question on gender differences in their work? This raises a question about the goals of gendered analysis of biomedical research: what can be achieved by interrogating the sex/gender division in current molecular medicine research? What is more, how can I avoid reinforcing the sex/gender dichotomy in my analysis? How to avoid stabilising the sex/gender division when I consider its relevance for systems medicine research? This question is especially relevant for feminist theory where the sex/gender division has been under scrutiny from the start.

4. Sex/Gender Binary in Scientific Research

As I concluded the part dealing with Longino's feminist virtues (part 2.5), gender medicine initiatives have been very helpful in this study when considering the ways in which possible gendered differences should be acknowledged in molecular medicine research. In gender medicine literature, concepts of sex and gender are used to refer either to biological or social reasons behind disease emergence or its treatment outcomes. However, sex and gender are also seen as intertwined, and separating them in medical research can be counterproductive. In the following section, I explain the reasons for which the sex/gender dichotomy has been under scrutiny in feminist scholarship, and how I understand gender medicine in relation to it. Finally, I will elaborate on how I have used gender as an analytical tool in this work.

4.1. Feminist Critiques towards the Sex/Gender Dichotomy

Whether a certain set of characteristics is something that individuals are born with, something they acquire through social relations, or something that is used to describe a certain group of people without much biological basis, has been an important question for feminist scholarship.

This debate has shaped feminist theory since the beginning of the feminist movement, when people started to question the assumption that women's nature would inevitably prevent them from having any role in the public sphere.[127] While first-wave feminism criticised the idea that the nature of women would prevent them from taking part in political action, second-wave feminism elaborated the criticism of biological essentialism. Feminist scholars pointed out how sexual politics, as Kate Millett puts it, used biological essentialism to support patriarchal power structures via its view on heteronormative, reproductive womanhood.[128] This criticism developed into a distinction between biological *sex* and social *gender* during the 1970s, which further highlighted the need to separate feminist politics from the idea of biological determinism associated with essentialism.[129] This criticism was not only aimed towards contemporary politics but many feminist scholars also pointed out how different social theorists, such as Karl Marx and Claude Lévi-Strauss, had theorised women's role in society in relation to reproduction.[130] While criticism towards biological determinism was the guiding light for second-wave feminism, the role of essentialism within feminist theory, defined in relation to universal womanhood, universal female oppression or female voice/language,[131] was questioned during the 1980s. By highlighting how "the technology of gender"—a term borrowed from Teresa de Lauretis[132]—informed feminist scholarship, social constructivist feminists pointed out that feminist theory represented white, middleclass, and heterosexual women. Thus, feminism largely overlooked how conceptualisations of, for instance, class, race,

[127] For example, Mary Wollstonecraft challenged Jean-Jacques Rousseau's view of the role of Sofie in *Émile* by pointing out how the characteristics that Rousseau described as part of female nature could be considered as a product of social education. See Wollstonecraft 1796.
[128] See Millett 1971. Betty Friedan's book *The Feminine Mystique*, which described the situation of housewives in 1950s America, has often been seen as one of the founding works in the second-wave feminism. See Friedan 1964.
[129] Simone de Beauvoir's argument "one is not born, but rather becomes, a woman" (Beauvoir 1956, 273) has often been used to highlight the need to separate between sex and gender.
[130] See, for example, Firestone 1979, MacKinnon 1989 and Rubin 1975.
[131] See, for example, Cixous 1986 and Gilligan 1982.
[132] De Lauretis coined the term in accordance with Michel Foucault's "technology of sex" in order to highlight how the sex/gender differentiation, too, was formed in relation to social discourses. See De Lauretis 1987, ix.

and sexuality affected women's lives.[133] Instead, social constructivist feminism, often connected with poststructuralism, started to interrogate the meaning of sex as well as gender, referring to scholars such as Jacques Lacan and Jacques Derrida.[134]

It is important to highlight that both the essentialists, who based the criticism of patriarchal social order to the idea of womanhood, and the social constructivist feminists, who went against the possibility of talking about womanhood in universal terms, critiqued the ways in which society oppressed women. Moreover, as Diana Fuss highlights, the polarised vision between essentialism and social constructivism within feminism was largely caricatured based on the primacy given either to the natural or social, assuming that "while the essentialist holds that the natural is *repressed* by the social, the constructionist maintains that the natural is *produced* by the social."[135] However, Fuss points out that this clear-cut distinction poorly represents the feminist scholarship of the time. For instance, many scholars who defined themselves as social constructionist did this by addressing "women" instead of "woman" and, thus, avoided the critique of essentialism without asking how their own accounts still were based on an essentialist framework. Moreover, Fuss states that the division of feminist theories according to the nature/culture polarisation is not sufficient since it cannot explain the complexity of the work of many feminist theorists.[136]

While it is important to stress that the discussion of sex/gender differentiation in feminist scholarship cannot be clearly viewed as a debate between essentialists and social constructionists, it is important to see the impact that sex/gender based analysis had for the feminist scholarship, including in feminist science studies. As noted, the feminist critique

[133] See, for example, hooks 1981, Spelman 1988, Wittig, 1992. The criticism of feminism gave rise to intersectionality that aimed to consider how not only gender, but also conceptions of race and sexuality took part in the oppression of women, see Crenshaw 1991.
[134] Fuss 1989, xii. Fuss states that Lacan and psychoanalysis have been important for social constructionist feminists, since instead of using sexual difference as a tool for explaining consciousness, it aims to explain the basis for sexual difference. See Fuss 1989, 6. Especially the works of Juliet Mitchell have opened door for a discussion between psychoanalysis and feminism, see Mitchell & Rose 1982.
[135] Fuss 1989, 3.
[136] Ibid., 4.

towards differentiation between sex and gender was not only aimed at feminist theories but also towards biological sciences. For example, Anne Fausto-Sterling argued that the differentiation between sex and gender created an assumption that biological sex difference would be unquestionable, thus limiting the number of genders to two.[137] Similarly, Judith Butler's notion of performativity, which is viewed as a one of the key terms of queer theory, highlighted how the biological category of "sex" could be seen as an outcome of socially defined gender.[138] As mentioned, from the late 1990s onwards, new materialist scholars have started to distance themselves from social constructivism which, in their view, disregards how materiality itself takes part in its materialisation.[139] The turn to materiality in feminist theory does not, however, mean the reintroduction of sex/gender dichotomy to feminist scholarship but, rather, biological sciences are used to further emphasise how this distinction makes little sense when biological organisms are seen as dynamically intertwined to their environments.[140] Thus, gender medicine's emphasis on the need to highlight sex and gender differences in medical research can sound rather dubious for someone having read feminist scholarship problematising and challenging the need for the sex/gender dichotomy. Further reading, however, shows how gender medicine aims to develop a more nuanced understanding of the basis of gender differences in diseases.

4.2.Sex/Gender in Gender Medicine

When considering the relevance that gender medicine has for my analysis, it is important to understand that the basis for its demands for studying sex/gender differences in diseases is in clinical information. As Vera Regitz-Zagrosek writes, "[c]linical studies are a cornerstone of

[137] Fausto-Sterling 1985.
[138] Butler 1990, 10, 1993, and 2004.
[139] See, for example, Barad 2003, Grosz 2004, Kirby 1997, and Wilson 2002 and 2004.
[140] See, for example, Frost 2014, Weasel 2016, and Richardson 2017.

Gender Research" as they "reveal a very large number of differences in clinical manifestations, in clinical presentation and in outcomes."[141] In other words, medical statistics show a clear discrepancy between genders in certain diseases, such as cardiovascular diseases. The problem, the proponents of gender medicine indicate, has been to assume that the treatment norm would fit both genders equally and that everyone would show similar symptoms of the disease. Furthermore, this norm is often based on male bodies as, for example, clinical trials excluded women's bodies due to menstruation and possible pregnancy. While legislation in many countries now requires medical professionals to perform clinical studies also with women,[142] proponents of gender medicine instead argue that understanding the importance of addressing possible gender differences already at the research design stage, including research done with animal models, is required.[143] This is because showing gendered differences in disease numbers or treatment outcomes between male and female patients does not explain where such differences come from. Thus, to study them requires a new research design that takes into consideration possible factors influencing gendered differences in these statistics.

Differences in clinical statistics can be the result of biological sex differences, societal gender roles or reflect the way in which sex and gender are connected and influencing one another. In other words, while gender medicine literature does make a distinction between sex and gender, it also emphasises that these two terms can be inseparable in some studies, as Regitz-Zagrosek and Seeland explain,

> On one hand, sex influences gendered medical roles, i.e. testosterone determines aggressive behavior that may be associated with risk seeking and neglection of prevention. On the other hand, gender roles, e.g. professional exposition to stress, poor nutrition, environmental toxins, or endocrine disrupters may lead to genetic or epigenetic modifications that differ in women and men.[144]

[141] Regitz-Zagrosek 2012, 3.
[142] Schiebinger 2003.
[143] See Regitz-Zagrosek & Seeland 2012 and Regitz-Zagrosek 2012.
[144] Regitz-Zagrosek 2012, 2.

The role of epigenetic changes has been especially emphasised in feminist new materialism as a possible connective point between feminist theory and life sciences.[145] What is crucial in this definition of sex/gender differences in gender medicine is that it allows a certain murkiness around the concepts of sex and gender as they gain meaning in relation to the studied disease. The concepts of sex and gender should not, therefore, be seen as fully stable in this literature. In relation to my own work, it is also important to remember that rather than trying to evaluate FIMM's research, my aim is to understand how a systems approach can be implemented in medical research design and how this reflects larger changes taking place in current biomedical research. In this approach, I argue, the concept of gender is a useful analytical tool.

4.3. Gender as an Analytical Tool

Due to the increasing value given to new approaches in biomedical research and possible future healthcare planning, I believe it is necessary for feminist scholars to engage with systems medicine research. This is essential to better understand not only why there is a need for studies that highlight biological complexity, but also how such medical applications challenge existing practices, and in so doing also require a new formulation of the relation between scientific research and society. In this research, I hope to show that gender is a useful analytical tool in examining the extent and hopes for such changes within the scientific community.

My goal in this research is a pragmatic one: I maintain the old indication of feminist science studies that gender can function as a useful analytical tool to question how scientific research is built and what are its aims. However, my research is not an evaluation of possible gender biases in molecular medicine research. Rather, I wish to comprehend how existing

[145] However, recent scholarship has urged caution towards taking epigenetic theory with its face value and, instead, engagement with scientific research is needed to show how, for example, sex differences are implemented in epigenetic research in a way that do not correspond with the idea of dynamicity, plasticity and complexity often emphasised in feminist scholarship. See, for example, Richardson 2017.

practices and aims in systems medicine research include and exclude gender in the research design and analysis in order to obtain, what Bruno Latour calls, "critical proximity"[146] to systems medicine research.

This means that my aim is not so much to explain why gender is not included into systems medicine research but to question what is meant by gender in such context, how the sex/gender difference is seen by researchers and how researchers view the rationale and possibilities to include gender into their research. This, I argue, will help to better understand how a systems approach is brought into medical practices, how this changes the goals of the research, and how the relation between an individual patient and the study of disease is seen. This is because gender as a concept is bringing together both the biological and lived experienced of human existence. As the gender medicine literature suggests, when trying to uncover the reasons behind clinical differences between recorded "male" and "female" patients, one cannot automatically prioritise sex over gender, or the other way around, as it might not make sense to fully separate these concepts when considering the reasons behind a disease. However, while gender thus frames my approach to systems medicine, the main aim during my fieldwork at FIMM was to examine how systems medicine research, which is one of the specialisation of the institute, is done in practice. Thus, my emphasis was to try to understand individual researchers' work, as they explained it, to gain insight on what kind of changes are seen in relation to systems medicine research; how it differs from previous molecular medicine approaches and how researchers dealt with biological complexity in their work. In other words, my main aim in my fieldwork was to follow a new materialist approach in engaging with science-in-making. In the next part, I elaborate how this approach shaped my research methodology.

[146] Latour 2005, 253.

Part II

Methodological Design

My research has been influenced by Haraway's, Latour's and new materialists' aim to engage with science-in-making. This means that from the early stages of this research project it was clear that I wanted to interview systems medicine researchers about their work and observe their daily research practices. Hence, I needed to find a medical research institution implementing systems biology approach into their research. This is how FIMM became the empirical focus of my research.

5. Description of FIMM

In 2003, the Academy of Finland put forward an initiative for establishing a new research institute that would focus on molecular biology.[147] Signed by respected molecular biology researchers from different universities as well as representatives from the European Molecular Biology Laboratory (EMBL) and the Academy of Finland, the debriefing aimed to convince the Ministry of Education that Finland should invest in the research centre that would work under the EMBL and in close collaboration with similar institutions planned in other Nordic countries. The big monetary investment was considered important in order to support the future of European biosciences, Finland's abilities to maintain high research profile in molecular genetics and for the development of Finnish healthcare infrastructure and technologies that could support enterprises also outside of academia.

[147] Initiative for the Establishment of a Molecular Medicine Research Centre in Finland in co-operation with the European Molecular Biology Laboratory (EMBL), The Academy of Finland 2003.

Finland was seen as a good location for a high-profile research institute focused on molecular medicine for several reasons. First, Finnish researchers, such as Leena Peltonen-Palotie, had a respectable international reputation in the field of human genomics and could, therefore, draw other high profile researchers to Finland if the right settings were provided. Second, Finland could provide a suitable context for molecular research given that previous investments in the Finnish Genome Centre, biotechnology centres and biosciences at the universities would provide the technology and knowhow needed. Finally, the existing research culture and local concentrations of biotechnology and medical research at the Meilahti medical campus in Helsinki, which was the suggested locale of the institute,[148] would make an active clinical collaboration possible. Following these points, the initiative suggested that the centre would be focused on human genetics and cancer biology as they are "two of Finland's strongest areas of medicine research".[149]

The result of the initiative, the Institute for Molecular Medicine Finland (FIMM) was founded officially in 2006 and in 2008 it began its operations in a building at the Meilahti medical campus at the centre of Helsinki. This three-floor building currently houses almost 200 employees as well as biobanking and technology facilities that are essential for the institute's need for storing and processing biological data. Essential for the daily research is also the close proximity, and connecting underground tunnels, to the clinics and university buildings at the campus area. Over ten years after its initiation FIMM is now a fully functioning research centre under the EMBL network and attracts researchers and graduate students all over the world with its international personnel and focus on human genomics and cancer-focused systems

[148] Meilahti was not the only option for the location of the institute as Turku also had a strong existing research culture and technological settings. In fact, in a report requested by the Ministry of Education in 2005, investigator Kimmo Halme suggests Turku as the place for the new centre. See Halme 2005, 46. The initiative by the Academy of Finland takes Turku into account as a possible location but highlights that the Meilahti campus has existing infrastructure, close proximity to university research centres as well as clinics and its location at the centre of Helsinki would also be compelling to international researchers who might bring their families with them.
[149] The Academy of Finland 2003, 19.

biomedicine. FIMM's aim to excel new systems approaches in its cancer research combined with its connection to the established history of Finnish molecular genetics research and cancer studies make it an excellent case study when examining how systems approaches operate in molecular medicine research.

6. The Research Methodology

While my study aims to form a feminist engagement with systems medicine through gendered analysis, it is important to stress that I intent to offer a sense of systems medicine research as it is seen by the researchers themselves. This aim was formed in accordance with feminist scholarship emphasising engagement with science-in-making (as explained in subsection 3.2). As Lynda Birke highlights in her interview with Cecilia Åsberg, the aim to understand the research goals in natural sciences is intrinsically linked with possibilities to form interdisciplinary research where scholars from different fields would try "to figure out how to talk to each other in ways that generate new ideas, and new methodologies."[150] Because of this, I have aimed to follow Bruno Latour's guidance in sociological research that underlines the need for sociologist to let research subjects define the rationale behind their own work. In other words, I have aimed to examine systems medicine as an emerging research that is currently taking place rather than as a set of established research practices. Thus, a central part of my research has been my fieldwork conducted at FIMM.

During autumn 2014, I spent four months visiting FIMM. At the time, there were 15 research groups at FIMM out of which eight were under the "systems biomedicine and precision therapeutics" and seven under "human genomics" specialisation. As a part of my fieldwork, I

[150] Åsberg & Birke 2010, 419.

visited six groups (Groups A–F) from the systems biomedicine side.[151] The biggest of them (Group A) focuses on individualised systems medicine, particularly on the study of acute myeloid leukaemia (AML), prostate, and ovarian cancer. One of the main focuses of this group is to take part in FIMM's "grand challenge" programs that aims to develop "individualised systems medicine" (ISM) in relation to AML and other cancers. The ISM project links multiple groups: Group B focuses on computational systems biology, Group C studies the chemical factors related to cancer systems, and Group D focuses on translational research (i.e. in creating direct links between basic research and the clinical treatment of patients). It is important to note that all of the groups were simultaneously working on multiple projects that were connected to individual researchers. It follows that co-operational relations between different groups were multiple and usually related to distinct projects. For example, some of the researchers from Group A were in close co-operation with Group E whose main aim was to create new imaging tools to study cancer cells or with Group F that focuses on studying lung cancer with the aid of mouse models.

I visited each Group (A–F) for one week, except for Group A where I stayed for two weeks. During these visits, I interviewed all the members of the group that were available as well as shadowed their daily research practices when possible. I was allowed to attend groups' weekly group meetings and other meetings they had. I also interviewed all the group leaders from the human genomics side, apart from two who were not available, as well as one whole group from human genomics side, since they collaborated with Group B. All in all, in 2014, I interviewed seventy-nine people of whom fourteen were leaders of a research group, eight

[151] I had interviews with the leaders of two smallest groups (Group G and H) but did not visit the groups, since their research was not linked to the rest of the groups nor larger systems medicine projects in the institute. The operation of these two groups in the institute have since terminated while the groups I visited during my fieldwork are still in operation when writing this in 2018.

senior researchers, three visiting researchers, three clinicians,[152] seven postdoctoral researchers, thirty doctoral students, six research assistants, six technicians and four project coordinators.

I focused on four themes in my interviews: (1) description of interviewee's own research, (2) co-operation within and outside the institute, (3) how they viewed their own research in relation to systems medicine/human genomics and (4) what they thought of FIMM as a working space. Interviews lasted from thirty minutes to one and half hour. The nature of semi-structured interviews made it possible to accumulate understandings of group dynamics with each interview, making it easier to clarify issues by referring to knowledge gained from prior interviews. Due to this, at the end of the fieldwork, the structural dynamics as well as informal aspects affecting co-operations within and outside the institute had become clearer. The nature of the semi-structured interviews also enabled more detailed questions concerning, for example, the role of gender in individuals' research when this was applicable.

I also participated in lectures and symposiums that FIMM organised as well as the presentations organised in the institute such as "Thursday's coffee sessions" where researchers (mostly PhD students and postdoctoral researchers) could present their own work to the rest of the institute. Given that I had a workspace at the institute during the fieldwork period, I was also able to observe the daily life at the institute as I spent my time working on my own writing and having coffee and food at the lunch area, when I was not conducting an interview or observing researchers' work. This meant that I could also have informal discussions with the researchers that helped me to gain a better sense of the daily work at the institute.

After going through my field notes and writing the first chapter drafts, I returned to FIMM in spring 2017 to conduct four follow-up interviews. One of the interviews was with the new leader of FIMM, another focused on pharmaceutical collaboration (with Researcher 8), and two on the potential benefits of including gender analysis into systems medicine research (one with

[152] These three people were at FIMM as researchers but due to their insights into clinical practices, they are referred to as clinicians in this study.

Researcher 2 and one joint-interview with Researcher 9 and Researcher 16). These interviews were deemed important to confirm and extend some of the issues raised during the fieldwork conducted in 2014. In addition, I interviewed professor Eva Gerdts, whose work in the University of Bergen has concentrated on studying gender differences in cardiovascular diseases, to gain a better understanding of how gender medicine operates in practice.

As noted, the main aim of my fieldwork was to gain a better understanding of how systems medicine research functioned at FIMM: how researchers explained their own research aims and how their studies were connected to the broader goals at the institute. In order to fulfil this aim, I followed Latour's suggestions for sociological research methodology. Latour's actor-network theory highlights the problem that many sociological studies have when they explain their fieldwork observations in relation to abstract concepts such as "society", leaving the reader unsure of what this means and what is its precise connection with the field. Instead, Latour argues, "the task of defining and ordering the social should be left to the actors themselves, not taken up by the analyst."[153] To establish this, Latour highlights the need for sociologists to let the actors of the study define themselves the groups they belong to and the aims of their research. This proved to be a useful guidance as already the first interviews showed that some group leaders listed under the systems biomedicine heading questioned what I meant by systems medicine research. Following Latour's advices,[154] I was able to form a more precise understanding of the differences as well as similarities between systems medicine groups by asking them how their research differed from human genomics research also conducted at FIMM. What is more, by asking the same question from the leaders of the human genomics research groups, I was able to see whether the view of these differences was shared.

Latour's warning against trying to explain researchers' aims in regards to abstract concepts such as "society" was highly relevant when writing this dissertation because I had to

[153] Latour 2005, 23.
[154] Ibid., 30–34.

consider how to form feminist engagement with a research field that appeared to be non-gendered. At the beginning of my fieldwork, based on my reading on feminist new materialist and gender medicine literature, I assumed that categories such as gender would be used to analyse individual differences in systems medicine research. However, starting from the first interview, it became evident that most systems medicine researchers at FIMM saw no relevance for categories such as gender in their ongoing research as they were working on a molecular-level. While increasing amount of feminist research is forming a gendered analysis of a molecular-level studies, these analyses are often based on research that already considers how molecular-level data could be linked with questions related to social embodiment.[155] In these cases, gendered analysis can offer a fruitful addition by critically examining the ways in which categories such as gender are produced in research. As I elaborate in Chapter 2, while the potential relevance of gendered approach was also noted by FIMM's systems medicine researchers, this was done either through a narrow scope of drug effects or as a future consideration that researchers were often unwilling to hypothesise in more detail because the discussion drifted outside of their expertise. Hence, I was faced with a question of how to approach these gendered silences in research without trying to explain them as a product of an abstract concepts such as "society" that Latour warns against.

Value-based analysis, as explained in subsection 1.2, has been an essential part of feminist science studies and is still highly relevant when considering possible obstacles in forming gender medicine initiatives. However, addressing gendered silences in FIMM's systems medicine research only as results of gendered research biases would do little in forming a sense of the challenges involved in including gendered approaches to molecular medicine research. Thus, this work aims to show not only why gendered analysis is relevant for present-day

[155] See for example M'charek 2005 and 2010, and feminist scholarship on epigenetics discussed in more detail in Chapter 5.

systems medicine but also what limitations research has to face to establish gendered approaches in systems medicine.

As FIMM's systems medicine researchers, at least at the moment, do not address gender differences in their research, my analysis is based on a comparative approach that considers systems medicine in relation to related research fields: human genomics, systems biology, personalised medicine, gender medicine, and epigenetics. As I explain in Chapter 2, this comparative approach is a result of my fieldwork as I noticed a striking difference between FIMM's systems medicine and human genomics research: Human genomics researchers all pointed out the necessity to always acknowledge possible gender differences in their research. Thus, in the end, gender became a useful tool in further considering the differences between human genomics and systems medicine research at FIMM. What I hope to accomplish through this comparative analysis is a sense of the importance of gender-based approach for systems medicine research. Moreover, I wish to show how gender analysis is useful when considering possible ways to form feminist engagement with an emerging field such as systems medicine that, at the moment, is not explicitly gendered.

7. Ethical and Practical Considerations

In this work, I refer to my interviewees by their institutional positions. I use the term "researcher" to refer to group leaders, senior researchers and visiting researchers, giving more detailed information about the person in the text.[156] For other interviewees, I use the terms "PhD student", "postdoctoral researcher", "clinician", "technician", and "coordinator" to give a sense of their work's connection to the institute. I am referring to my interviewees through their institutional positions because some of my interviewees asked to remain anonymous. The use

[156] In this work, Researchers 1–11 are group leaders and Researchers 12–17 are senior researchers in their groups.

of titles rather than names is to especially protect the anonymity of PhD students, some of whom were very concerned of any possible harm their answers could have for their career prospects. The use of statuses and additional information in the text aims, still, to give a sense of people position in the institute to explain possible differences in perspectives, especially when discussing more general research aims of the groups.

As my interview cohort was international, I had interviews both in Finnish and in English. Unless otherwise noted, all the translations in the dissertation are my own. In my translations, I have aimed to be as loyal to the original meanings of the words as possible, following current medical literature. Still, I have marked when the citation is based on my translation to avoid any misrepresentations.

Chapter 2

Gender in Molecular Medicine Research

Comparing Human Genomics and Systems Medicine Research

On 8 of May 2014, I took the tram number 4 in the city centre of Helsinki. The tram took me to the Meilahti medical campus, where FIMM resides. I had contacted the leader of the institute in March of the same year and asked to meet him to discuss a possibility to conduct a fieldwork at their institution. In my introductory email, I had explained my wish to familiarise myself with the systems medicine research done at FIMM in order to learn how systems biology approaches are implemented in medical research. The reply was a short "this should be fine" and a suggestion that I would also arrange a meeting with Researcher 1, who was the principal investigator of Group B, with a background in systems biology research. Due to scheduling, my first meeting at FIMM was with Researcher 1. His group focuses on mathematical and computational analysis, and they also help other groups at the institute in mathematical modelling.

FIMM's building is close to the tram stop. I entered the building and explained to the receptionist why I was there. He called Researcher 1, who came to meet me at the lobby and led me one floor up to his office. I took a seat next to the table in the office and started the interview. After inquiring about the background and framework of their research, I asked "how do you consider categories like gender in your research?" He replied that categories such as gender are factors that are part of personalised medicine but systems medicine research at FIMM is concentrated more and more on research on a molecular level. He then continued to explain how they use high-throughput drug screening as an individualised approach for cancer treatment. This left me perplexed as the link between molecular medicine research and

personalised medicine—and, thus, the relation between gender and systems medicine—remained unclear.

Responding to my request for clarification on the issue, he elaborated on how he sees categories such as gender from the point of view of computational modelling,

> You can divide [modelling] into three phases: pre-processing, where data is purified from all technical variation that is not connected to a disease or biology or genetics, so it is technical variation due to the measurement procedure (…) When that's done we hope to have only biological variation in the data, which is connected either to the disease or other biological variation between individuals (…) Next we have to decide whether we want to include that variation, which is real biological variation but not connected to the disease, or do we want to normalise that out. And normally we focus on mechanisms of disease and so we aim to normalise all age-, gender-, and other variations so that we can access the basic disease mechanisms. But, of course, when we want to project back to the individual, that all has to be included.
>
> (Researcher 1, my translation)

This first interview left me with many questions that would remain throughout my fieldwork at FIMM. What did it mean to "normalise" biological variation out of the analysis? How was this kind of information, then, brought back when "projecting back" to the individual? It was clear starting from this interview that although differences between patients based on gender, age, and other variants were relevant for personalised medicine—as they needed to be considered when treating an individual—they had little role on the molecular-level analysis in systems medicine research at FIMM.

I had been eager to ask about gender in systems medicine research in my first interview because my starting hypothesis was that researchers at FIMM would also consider possible gender differences in diseases as way to understand variation between patients. This hypothesis was based on my reading on gender medicine literature, underlining the importance of gendered analysis in medical research, including analysis at the cellular level. However, my interview with Researcher 1, as well as my fieldwork at the institute later in the autumn of 2014, showed that most of the researchers affiliated with systems medicine had little or nothing to do with categories such as gender in their daily work. Rather, as Researcher 1 explained, their studies

were focused on understanding the basis of cancer mechanisms. Even Researcher 2, the principal investigator of Group D specialised in translational research and personalised medicine, and who had a close collaboration with clinicians, said that they have not included gender differences in their analysis.

A striking difference in answer, likely owing to different roles in the institute, came from Researcher 3, who shared the role of principal investigator of Group D with Researcher 2. When asked whether gender had a role in his work, Researcher 3 replied, "absolutely: I have never seen a clinical study that didn't have gender included because it would be extremely stupid." While these two researchers share the role of principal investigator, their relation to Group D is very different. Researcher 3 is named as the principal investigator because the group was formed around his professorship. However, according to him, he was "much too old" to start a group and, thus, Researcher 2 runs the everyday practices of the group. Researcher 3's role at the institute, meanwhile, is more connected to the overall strategic planning of the research. He works in close collaboration with the leader of the institute as well as researchers from the human genomics side. Because of this role, Researcher 3's work in not limited to systems medicine research at FIMM. Rather, he considers future research strategies, which take into account two different research specialisations of the institute: systems medicine and human genomics. His answer about the importance to include gender in research can be better understood when compared to the similar reactions of the group leaders of the human genomics side. The need to include gender differences in research, hence, seemed to be a differentiating factor between systems medicine and human genomics research at FIMM.

My comparative analysis of human genomics and systems medicine research at FIMM in this chapter aims to explain the difference in answers regarding the consideration of gender differences in research. I start with a description of human genomics research at FIMM, which I trace back to the work of Reijo Norio and the formation of the idea that the Finnish population

is more genetically homogenous than most populations. This historical account helps to explain how knowledge of gender differences in diseases is acknowledged in FIMM's research. At first it seems that the difference between the human genomics and systems medicine approach in studying gender differences in diseases is immense. Gender is always mentioned in studies on population and family level in human genomics, as clinical studies mark the amount of female and male patients. In contrast, as Researcher 1 emphasised, systems medicine research at FIMM normalises gender variation out of the data as it focuses on cancer genome itself, aiming to understand underlying disease mechanisms. However, a closer look into the research practices shows that this difference is not so striking when considering researchers' possibilities *to explain* possible gender differences. While in human genomics gender is always mentioned as a part of clinical information, the basis for gender differences is seldom further studied. I will show, following arguments made in gender medicine literature, how addressing gender differences in diseases requires new research designs and data collection that would acknowledge both the biological and social aspects of gendered differences in diseases. I will conclude that considering reasons behind gender differences are also relevant for FIMM's systems medicine research because of the research's link to clinical practices, with possible gender differences in treatment outcomes.

1. Historical basis for Human Genomics Research

This part traces the history of the concept of "the Finnish gene pool", showing how it is based on the studies on the Finnish Disease Heritage (FDH). Understanding how the idea of the Finnish population isolate was founded in medical research is important when examining human genomics research at FIMM. This became clear when I interviewed Researcher 7, the leader of the human genomics specialisation at FIMM. He highlighted that the foundations for

their research field are the history of the Finnish population isolate, the organisation of healthcare in Finland, and the collected epidemiological studies. I will first trace the history of the idea of the Finnish population isolate to the work of doctor Reijo Norio who was a central figure in research on FDH.

1.1.The Beginning: Finnish Disease Heritage

A central event for the forming of the idea of the particularity of Finland's population genetics happened in the university of Helsinki's Children's Hospital in the 1950s. This is when doctors noticed recurring cases of newborns with nephrosis. Nephrosis is a kidney disease, which doctors had never seen, nor heard, emerging in newborns. Standard cortisone treatment did not stop any patient from dying.[157] In 1963, a 29-year-old doctor Reijo Norio was selected to examine any possible aetiology of the disease.[158] It was important to track down the ancestry and near relatives of the known cases as preliminary studies suggested that the disease could have a hereditary basis. While visiting the homes of the known 39 families in which the disease appeared in babies, Norio discovered 18 other cases. This reinforced the hypothesis of the hereditary basis of the disease, leading Norio to conduct a genealogical study of all the 57 families.[159] Norio's research, which used church records to trace family lineages as far back as the seventeenth century, became the foundation of the "Finnish gene pool".

Norio's research established congenital nephrosis (CNF) as a genetic disease. It showed that 28% of the parents whose child was born with CNF were relatives. In addition, tracing the family genealogies showed that many CNF parents had the same ancestors as another family's parents. These family relations were usually distant, tracing back to even eight generations, to

[157] Norio 2000, 13.
[158] Norio recalls this appointment by describing how he met a colleague Kauko Kovalainen on the corridors of the Children's Hospital who pointed at him and declared "you will go!" as "the wise had decided that someone should travel around the country and interview all the 39 known cases." See Norio 2000, 14. My translation.
[159] Norio 2003a; 442–444.

the 18th century or earlier.[160] This was enough to assure Norio that CNF was a genetic disease. After CNF, other diseases that did not follow any known disease description were investigated in a similar manner and in 1972, after 11 other diseases were identified to follow a similar logic, the concept of the Finnish Disease Heritage (FDH) was formed.[161] Today, FDH refers to 36 rare diseases. These are rare diseases as most of them are autosomal recessive disorders, meaning that the disease occurs only if both parents carry the same recessive genetic mutation and the child inherits the abnormal version of the gene from both parents. As they are much more prevalent in Finland than anywhere else, researchers looked for their cause from the population history of Finland.[162]

Crucial in the explanation of the origins of FDH is the term "founders effect", a kind of a bottleneck phenomenon, that helps to explain why certain genetic traits are multiplied in a particular region. This became a central term in FDH as most of the disease cases were connected with the areas of Eastern and Northern Finland that were settled by Finns only from the 1500s onwards. As Norio states, the inhabitation of these areas increased extensively in the 16th century largely due to the political agenda of the Swedish king Gustavus Vasa, who wanted to increase both the influence of the Crown in the uninhabited areas near the Russian border and the number of the households that would pay taxes to the king.[163] Noting that many FDH patients shared an ancestor that inhabited this area, Norio put forward the hypothesis that many of the recessive gene disorders, later listed as causes of FDH, arrived to the area with some of the first inhabitants.[164] The settlers, some of whom carried the recessive gene disorder and were thus not afflicted by the disease, had always a 50% chance to transmit a gene variant to their progeny. Due to the large family sizes and inhabitation of new Eastern and Northern areas of

[160] Norio 2000, 18–19.
[161] Perheentupa 1972 and Norio, Perheentupa & Nevanlinna 1973.
[162] Norio 2003a, 442–443.
[163] Ibid.; 442–446. Finland was under Swedish rule from circa 1150 to 1809, when it became an autonomist part of Russia. It became an independent country in 1917.
[164] See Norio 2000; 27, 46–49.

Finland by the descendants, more and more people in a larger geographical area also had recessive genes that carried the disorder.[165] Due to geographical isolation of the people, a bigger proportion of inhabitants would have a recessive gene causing disorder, making it more plausible of a child inheriting the same recessive gene disorder from both parents and, hence, the disease.[166] Thus, Norio explains, in Finland the relatively high number of these diseases in most cases is not a result of inbreeding between near relatives but a long geographical isolation of people whose ancestry inhabited the land from 1500s onwards.[167]

To understand why Norio does not talk about areal differences but of "the *Finnish* Disease Heritage", it is central to consider how Norio sees the geographical isolation of the areas connected to FDH as a result of Finns' difference to neighbouring Russians.[168] What is crucial for Norio's argument, in order to see FDH as a result of national biological heritage, is the idea of socially guided reproductive actions. Norio's broader framework connects his own research to other genetic, linguistic and cultural studies categorising Finns as a distinct population. This specificity is emphasised in FDH literature as the population isolate is explained in terms of cultural and linguistic specificities of the Finnish population.[169]

Norio's study had a lasting legacy on the research. His dissertation about CNF triggered a popular interest in hereditary diseases among the Finns that resulted in the Väestöliitto (The Family Federation) founding a new unit of Medical Genetics in 1971, with Norio as the chair.

[165] Norio 2000, 26–29.
[166] Ibid., 46–49. See also Peltonen 1997.
[167] Ibid., 34–39.
[168] Norio dedicated one article to discuss the genetic roots of Finns to emphasise the national specificity of FDH. See Norio 2003b. It is notable that studies discussing the genetic specificity of the Finnish population refer specifically to Finnish speaking Finns, often noting the genetic differences and similarities to national minorities such as Swedish speaking Finns or Sami people. See, for example, Nevanlinna 1972.
[169] See Norio 2003b; de la Chapelle 1993; Peltonen 1997; Peltonen, Jalanko & Varilo 1999. Seen this way, the notion of the "Finnish Disease Heritage" is deeply gendered as the family heritage played a crucial role in the definition of FDH. The concept of the family was a connective factor between urban and rural Finland. Although many of the disease carriers had lived in a city their whole lives, their family genealogies showed that in most cases their grandparents came from the sparsely populated areas of Finland. Following this logic, Norio notes that "the birthplaces of the grandparents represent the 'domiciles' of the disease genes, whereas in the maps of the patients and parents, the migration during the last decades to towns and to the south disturbs the original geography." (Norio 2003a, 448) It was possible to talk about a Finnish disease heritage only after the notion of the family heritage was tied to the population history of Finland.

As the main researcher, Norio's influence has been immense: even now, half of those specialising in medical genetics are former students of Norio.[170] The importance of the history of FDH for the human genomics specialisation at FIMM became clear in my interview with Researcher 4, a leader of one of the human genomics research groups. He suggested right at the beginning that I should read Norio's book to understand the foundation of their work.

However, when considering the connection between FDH and human genomics research at FIMM, it is crucial to take into consideration that most of FIMM's research focuses on complex diseases, such as diabetes, schizophrenia, cardiovascular diseases, migraine, and multiple sclerosis. Diseases linked with FDH are mostly caused by a mutation in one gene pair where recessive genetic disorder has been inherited from both parents, whereas complex diseases can include hundreds of mutations (both in the genes and the non-coding parts of the genome) that take part in the emergence of the disease. What is more, many complex diseases studied at FIMM are influenced by a combination of genetic and environmental factors, such as individual's eating habits. To understand why Norio's work is so important for FIMM's research, it is necessary to examine why researchers started to consider the possibility that the history of the Finnish settlements might benefit the study of more common diseases.

1.2. From the Finnish Disease Heritage to the Finnish Gene Pool

The journal *Tieteessä tapahtuu* (Happening in Science) published in August 2004 an article "Suomalaiset geenit hyötykäyttöön" (Benefitting from the Finnish Genes), where the authors Kirsti Käpyaho, Leena Peltonen-Palotie, Markus Perola and Tero Piispanen defend the idea of forming a national institution with a biobank. They argue that this institution would be essential

[170] Kääriäinen 2006. Norio's role in the development of medical genetics in Finland was honoured in 2013 by naming a new research centre, merging the Rinnekoti Foundation's Rehabilitation Home for Children, the Genetics Services unit and Family Federation's Medical Genetics unit, as the Norio Centre.
See: << http://www.vaestoliitto.fi/in_english/genetics/>> [Accessed 26.1.2018].

in order to use the Finnish epidemiological studies, collected by the National Institute for Health and Welfare (THL) and different universities over the years, in the studies of common diseases such as diabetes. They state that Finnish data offers specifically interesting potentialities for disease research since the data is well covered, including the tissue samples and family histories of studied individuals as well as description of their lifestyle and living environment. In addition, the authors highlight that Finland has a long tradition of collecting extensive population health statistics that could be used in research. However, they argue that collected records are not the only advantage that Finland has in biomedical markets, but that the homogeneity of the Finnish population makes it easier to locate possible factors that cause diseases.[171] This argument was based on the notion of "the Finnish gene pool".

The genetic basis of FDH, which was reinforced by the molecular genetic research in 1980s as distinct gene mutations were identified, not only strengthened the view of Finland's history as a cause of distinct diseases but also enabled researchers to consider Finland as a site that could be employed in the study of more common diseases.[172] As Leena Peltonen, Petra Pekkarinen and Johanna Aaltonen state in their 1995 article on the Finnish gene pool,

> [I]n the design of research strategy for any common disease, unique isolated populations offer special advantages. Especially valuable are populations in which population history and genealogical data on families or individuals carrying the particular trait can be reliably obtained from church records and a high quality of health care guarantees reliable clinical information.[173]

Although the term "Finnish gene pool" is not only related to the cases of FDH, the idea of the homogeneity of the population cannot be seen separate from it. Research on FDH was established around the idea that the Finnish culture, geography, and history had affected the

[171] Käpyaho et al. 2004, 5-8. All the authors are connected to biochemical research or marketing of life sciences in Finland. Especially Leena Peltonen-Palotie (known also as "Peltonen", or "Palotie" in Finnish publications) is well known in Finland since she was one of the world's leading researcher in genetic diseases. She was also a known public figure, who was often seen in TV interviews commenting and explaining scientific issues such as cloning. She had a central role in FIMM's founding and operation before her untimely death in 2010.
[172] Kestilä et al. 2010, 2311.
[173] Peltonen at al. 1995, 703.

biology of the individuals in the scale of the whole population. In addition, it has shown that Finland offered a suitable ground for gaining a genealogical understanding of diseases due to the existence of church registries and clinical records.

FIMM's human genomics specialisation has established the plans made by Käpyaho et al. in their 2004 article. The next section elaborates on how history of the Finnish population genetics is linked to human genomics research at FIMM.

2. Human Genomics Research at FIMM

The conceptualisation of the Finnish gene pool, epidemiological studies, and the organisation of the Finnish healthcare form the basis for FIMM's human genomics research on complex diseases. This means that the Finnish population is at the focus of research. As Researcher 7, who is also the leader of the human genomics side, emphasised, "at the moment, our research designs are based on asking whether a certain gene variant is more common in Finland than it is in other parts of Europe. (…) whether such gene variants are enriched in Finland or disappeared, selected against." In this part, I will explain how this research rationale is conducted in genome-wide association studies (GWAS), with an example of multiple sclerosis research at FIMM. I will explain the seen benefits of such statistical approaches for healthcare practices with the examples of Kardiokompassi pilot study and drug development. I will also point out shortcomings with the GWAS approach, especially the challenges linked to studying heritability.

2.1. Usefulness of Finnish Population Data in GWAS

Multiple sclerosis (MS) is an autoimmune disease in which patients' immune system starts to attack their own tissues. Studies have shown that MS cases are linked both to unknown environmental and genetics predispositions, as is the case with many complex diseases.[174] MS, as Researcher 5, who is the principal investigator of the group focused on human immune disorders, stated is "a very complex disease and taking place in the brain so an individualised medicine approach to it is not yet easy, or even possible." However, she continued, "what we have been able to do is, with our international collaborators, is to identify many genes, or areas of the genome, that predispose people to MS." To do this, they have used GWAS approach with a specific focus on particular areas in Finland. The GWAS approach enables researchers to map out the possible genomic loci associated with the disease. This approach identifies genomic areas that are shared by the patients but not by healthy people. It has been used only a little over a decade and is based on insights gained from the Human Genome Project (HGP).

Understanding single nucleotide polymorphism (SNP) level differences is pivotal for the success of GWAS studies. As noted in the previous chapter, the HGP revealed that humans had much less genes than expected, which pushed the research into considering interactions within and between the cells. Mapping out the human genome also formed the foundation for comparing genomic differences between individuals. As Barkur Shastry writes, "in two randomly selected human genomes, 99.9% of the DNA sequence is identical. The remaining 0.1% of DNA contains sequence variations."[175] The human variation, thus, is explained at the SNP level by mapping out single alleles in the DNA that are different between individuals. As these SNPs are considered to be "stable and not deleterious to organisms"[176] they are used to account for heritable variation between individuals. This way, SNP variation can also help to

[174] Saarela et al., 2006.
[175] Shastry 2002, 561.
[176] Ibid.

explain "the genetic basis of the most common familial traits, evolutionary processes, and complex and common diseases such as hypertension, diabetes, obesity, and psychiatric disorders."[177] The aim of GWAS studies is to locate SNPs associated with the studied disease.

As Nikolas Rose accounts, SNP studies were also used to explain differences within and between populations that could be used, for example, in disease studies. The fact that all humans share such an extensive genomic similarity, not to mention 98% similarity with chimpanzees, questions any possibilities to talk about race in genetic research. As Rose has argued, the emphasis has shifted from race to population differences.[178] Identifying SNPs during the HGP put forward another project, "HapMap", in which the aim was to identify inheritable collections of SNPs in a chromosome.[179] These sets of SNPs are called haplotypes. To locate haplotypes, the "HapMap" project compared genomes from different populations, defined according to their geographical population history.[180] These extensive haplotype identification studies also enabled later GWAS studies by offering a comprehensive map of possible haplotype linked SNP variations. Mapping them was seen as beneficial for disease studies as haplotypes help to distinguish group specific variation.

In GWAS an association between genomic loci and a studied disease is based on a comparison between patients' genome and healthy genome. If a SNP is shared by patients but not with the healthy cohort, it is associated with the disease. Because of the haplotype mapping, which has already formed an understanding of how different SNPs are possibly linked, "each GWAS-associated variant will typically have hundreds to thousands of other variants which are also significantly associated with the trait."[181] While comparison in GWAS between genomes is not focused on particular genomic loci, thus making the GWAS studies "unbiased with

[177] Ibid.
[178] Rose 2007, 168.
[179] The definition of collection in relation to haplotype was done via linkage disequilibrium (LD) phenomenon. Witte 2010, 1. For more information on LD, see Slatkin 2008.
[180] Rose 2007, 168–169.
[181] Hormozdiari et al., 2015, i206. See also Visscher et al. 2012, 9.

respect to prior biological knowledge"[182], the prior work done in the mapping of haplotypes functions as a basis to evaluate which SNP associations are linked to the disease and how their relation to the disease is understood.[183] The importance of GWAS, as John Witte explains, is based on its abilities to "detect small to modest effects" and it has uncovered many new disease associated SNPs in the genome, both in genes and in the non-coding regions of DNA.[184]

While the genetic homogeneity of the Finnish population is considered as an asset in GWAS studies, GWAS can produce statistically relevant results only if the number of compared samples is large enough and the more there are samples, the more there are also identified variants.[185] This is why, as Researcher 5 emphasised, their research on genomic loci associations on MS depends on international collaboration,

> We are part of both Nordic and international MS consortiums, which has been the only way to find gene variants in these kinds of diseases where they are risk genes. For that kind of research, you need large patient cohorts. From the 100 MS associated genes, that we now know, we have found almost all of them in the frame of this consortium. That shows the power of collaboration. (…) International collaboration really is the only option in the study of complex diseases in order to gain the power to recognise the variants that have the real association. No one can do that alone.[186]
>
> (Researcher 5, my translation)

Researcher 5 points out that Finnish population data has been useful in MS research as "in Finland MS disease has been enriched to Southern Ostrobothnia region where there are clearly two times more MS cases than in other Northern European populations." Similarly to FDH cases, the assumption is that the historical bottleneck phenomenon has enriched genetic predisposition to MS in this particular region. This view is supported by the fact, as Researcher 5 explains, that "there are more families where you have multiple MS patients whereas usually MS patients report that they don't have any other family member with MS." Researchers studying patients from this region, stress that population genetic isolates can help to study rarer

[182] Visscher et al. 2012, 9.
[183] Ibid.
[184] Witte 2010, 2.
[185] Visscher et al. 2012, 10–11.
[186] See Sawcer et al. 2011 for the general publication of the research results of the consortium.

SNPs that have been associated with MS but, due to the large cohorts used in GWAS studies, seem to have only a modest association with the disease. Studying population isolates can help to evaluate the importance of rarer variations in distinct populations.[187] This is one reason why FIMM's research design, as noted by Researcher 7 in the statement at the beginning of this subsection, is based on asking how the specific history of Finland can aid the research on complex diseases.

While FIMM's human genomics research is focused on studying genetic predispositions, environmental factors are also seen significant in the formation of the disease. For instance, Researcher 7 stressed that the associations between the disease and areas of the genome can help to focus future research: "in the ideal situation, [we could learn] what kind of genetic predisposition is susceptible to a certain kind of environment. A simple example of this is when certain drugs are not suitable for some people as they metabolise them differently, so we have to administer different kind of doses." In these kind of cases, the study of disease associated genomic loci can help to direct future research towards more personalised treatment and prevention strategies. FIMM's human genomics research is seen to support the development of personalised medicine especially through the improvement of disease risk calculators and drug development.

2.2. Population Genomics in Disease Risk Calculation and Drug Development

As the research done by Researcher 5's Group shows, one central element in FIMM's human genomics research is to identify genomic regions associated with the studied complex diseases. This kind of basic research gives the basis for the more applied uses of genomic information in disease risk assessment, disease prevention, and drug development. These kinds of initiatives

[187] See Kallio et al. 2009; Jakkula et al. 2010; and Mero et al. 2010.

show well the foreseen benefits that gaining further information of the genomic associations of diseases can have for the more personalised treatment options.

One example of using population genomic data to support personalised disease prevention is KardioKompassi project, a pilot study conducted by FIMM and the blood service of the Finnish Red Cross in 2014–2015.[188] The project's goal was to further develop disease risk assessment on cardiovascular diseases. FIMM's role was to implement information of the known genetic association of PCSK9 gene region with coronary artery disease to the previously existing FINRISK internet database, which calculates individual risk for developing cardiac diseases and stroke. FINRISK is based on information gained from three cohorts started, respectively, in 1982, 1987, 1992, each of which continued for ten years. Each cohort contained samples from people, aged 30 to 64, from three different regions of Finland, including information about smoking, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes, and family history. In total, close to 20,000 men and women have taken part to the studies. This data was then processed to form a basis for an individualised risk assessment that can be freely used on the internet by all healthcare workers, offering a ten-year estimate of the possibility for the patient to develop coronary heart disease, stroke, or their combination.[189] The aim of FIMM's KardioKompassi pilot project was to add the known genomic association information of coronary artery disease to this database so that the risk assessment could be even more individualised.

One of the biggest benefits of the project was the ability to deepen the risk assessment, especially for young people. Due to their age, the risk assessment for young people remains low even if they smoke, have high blood pressure, and family history with cardiac diseases. By adding their individual DNA sequencing data, gained from a blood test, the database is said to

[188] For the description of the project, see < https://www.sitra.fi/en/articles/cardio-compass-towards-better-cardiac-health-genome-data/> [Accessed 26.1.2018].
[189] Vartiainen et al. 2016.

offer a more precise and long-term risk prediction, also indicating how the risk grows when ageing. This is hoped to encourage earlier prevention tactics by showing people how, for example, quitting smoking can reduce their total risk even if they have genetic, and other, risk factors.[190] After the success of the pilot study it is now followed by a larger study, called GeneRisk. The duration of the GeneRisk project is 20 years, with an aim to follow-up the link between genomic information and health.[191]

Another possible way to use population genomic data to benefit healthcare is via drug development. Unlike in KardioKompassi project, in drug development, the research might not only be focused on genetic regions associated with a disease but it can also benefit from the study of genetic mutations that seem to prevent emergence of certain diseases. Here, the approach to genomic data is different from previously explained disease studies, as it is not focused on any particular disease. Instead, Finnish DNA sequence data is used to further study deleterious genomic variants that have been noted in the previous studies. FIMM's researchers have made such an association between LPA gene and heart disease. As Researcher 4 explains, after mentioning the benefits of population data in studying complex diseases such as schizophrenia,

> Another example [of using population data] is from the study of heart disease and LPA gene, which has a variant, which knocks down the gene. [In our studies] there were two variants, one of which was clearly more common in Finns and in this case the dynamics was that it influences a protein that can be measured from the bloodstream, named LP(a). (…) [LP(a)] is a tracer, which is also used when predicting heart disease and in this case it knocks the protein production on. Those who have gotten such a gene variant to their genome from both their mother and father, have their blood's LP(a) levels close to zero. What makes this interesting is that these people seem to have a lower risk for heart disease. So this is not a risk variant but actually a protective variant. In this case, the fact that LPA gene gets broken suddenly protects us from getting a heart disease. And again, this is enriched to Finland so now there is a subgroup in Finland who has this feature.
>
> (Researcher 4, my translation)

[190] Ripatti & Widén 2016.

[191] The GeneRisk started in 2015 and finished collecting participations in 2017. For the description of both KardioKompassi and GeneRisk project, see: <https://www.fimm.fi/en/research/ongoing-collaborative-projects/personal-genomics-projects>[Accessed 11.1.2018] More information of the GeneRisk project can be found (in Finnish) in << http://www.generisk.fi/content/generisk-tutkimuksesta>> [Accessed 11.1.2018].

Researcher 4 explains the possible therapeutic usage of LPA variants information by stating that,

> There are two ways in which it could help our health. First is that these kinds of variants and genes are very good when developing drugs or therapies because they protect. So we have direct [information], or at least the first estimate of the mechanistic routes for it, that if we don't have this protein production, we have less risk to get a heart disease. So in that case a prodrug that would lower the amount of that protein in our bloodstream could probably work in a similar manner and it could help—like we have statin for lowering cholesterol. Then there's another way, or another thing we can derive from it, which is that because we have people with this knock-down gene walking in the street, and functioning normally in the society—or at least that's how it appears—this gives us information that it is not awfully fatal to have this [gene] knock-down. So, from the viewpoint of drug development, we could think that this kind of drug target would be relatively safe because in a way it is an outcome of a natural experiment as these people are nevertheless reproducing and functioning in the society. This could be helpful for classical drug development.
>
> (Researcher 4, my translation)

The LPA example shows how important it is for FIMM's research to have an access to population based data: Good national health statistics together with the homogeneity of the Finnish population helps to locate the interesting genetic mutations. In addition, the fact that people live with these mutations function as a kind of proof-of-principle that a drug mimicking the effects of the mutations could be potentially beneficial for the individual with little side-effects.

To benefit research that uses Finnish population genomic data, FIMM has started the Sequence Initiative Suomi (SISu) project that brings together DNA sequence data, gathered in different individual studies both in Finland and abroad that use Finnish population health data.[192] Data was collected via national health studies (such as FINRISK) and via projects focusing on specific diseases (such as MS). By putting together this DNA sequence data,

[192] See <http://www.sisuproject.fi/> [Accessed November 16, 2016]. The name "SISu" has likely been chosen (especially considering the mix between English and Finnish in the title) because "sisu" is seen as a characteristically Finnish word. It has no exact English translation but it is seen to describe particularly Finnish character of will power and determination even when against all the odds. In this sense, the project name "sisu" can be seen to emphasise the data being characteristically Finnish.

accessible both to Finnish and foreign researchers,[193] FIMM's researchers aim to aid studies that could locate and better understand genome variants (such as those linked to the LPA gene). This is seen to benefit individualised healthcare either through projects such as KardioKompassi or drug development.[194] In this light, it is easy to understand why one emphasis on human genomics at FIMM is to produce Finnish sequence data that can be compared with international patient cohorts. While GWAS approach has been applauded by FIMM's researchers for its abilities to show genomic loci association in complex diseases, some challenges have also been noted.

2.3. Challenges in GWAS studies

GWAS is the basis for most studies done at FIMM's human genomic research. However, it has its own issues that limit the possible questions that can be answered with the data. One of the biggest troubles has been to examine "the causal factors underlying GWA study results."[195] This difficulty came up also in my interview with Researcher 5. MS is a complex disease not caused by one gene mutation, she explained, and GWAS analysis also shows the relevance of non-coding areas of genome.[196] As Researcher 5 notes, "the found associations are usually in the non-coding region and probably regulatory elements. Therefore, it is difficult, even if

[193] While the data is available through the SISu web search, this only contains summary data of the cohort and sequence information. To access the cohort data more broadly, researchers are required to apply access through the biobank, which stores and handles the cohort. This means that the broader phenotype data, restricted by the biobank legislation, is accessible also for all researchers, both in and outside academia, but they have to go through an application process where the access to data is considered in relation to a specific research proposal. Biobank services also cost. For further information about the biobank data access policy, see < https://www.thl.fi/en/web/thl-biobank> [Accessed 26.1.2018].

[194] The importance of population data was recently emphasised as a new large study, FinnGen, was launched in 2017. This project, in which FIMM is actively involved, is a collaboration between University of Helsinki, hospital districts, the National Institute for Health and Welfare, Finnish biobanks and multiple international pharmaceutical companies. The aim is to use Finnish genome data together with clinical data to better understand disease mechanisms. The aim is to collect 500,000 samples by the year 2023. For more information, see <https://www.finngen.fi/en> [Accessed 26.1.2018].

[195] Witte 2010, 8. GWA means the same as GWAS. Also GWS is used to refer to GWAS.

[196] The non-coding area of DNA was, prior to the results of the Human Genome Project, erratically termed as "Junk DNA" as it was thought that only protein coding genes would have an active role in the forming of a particular phenotype. For more of the history of the "Junk DNA" see Bardini 2011 and Carey 2015.

something is found from this region, to show what their function is and what they do." This comment highlights how the relevance of the non-coding region of the genome in MS linked associations also makes it difficult to study; it is challenging to study further and validate what kind of part these mutations in the non-coding area play in the overall emergence and existence of the disease. The focus on Finnish population isolate, as described in subsection 2.1, can help to clarify the role of rarer mutations but even so, creating functional models is troublesome. This is a clear difference to diseases caused by a single gene mutation as it is easier to perform functional tests and create animal models when it is possible to see what kind of change a mutation in a gene would make in an organism.

In order to cope with this challenge, Researcher 5's Group is focused on studying gene associations with the assumption that it would help to gain more information about the basic mechanisms of MS. This reasoning is connected to Researcher 5's other studies on primary immune deficiencies (PIDD) that are monogenic (caused by a mutation in one gene). As she explains:

> [The fact that it is easier to study what happens when a gene doesn't work] is on the background of this idea, to find monogenic models also for autoimmune diseases, because one central symptom of immune deficiency is autoimmunity so we're able to understand what causes this autoimmunity. It is probable that if this protein, for example, causes certain cell types to differentiate and then if we're suddenly missing the regulatory immune cells, we're left only with active killer immune cells, but not regulatory ones. This could be one mechanism that causes autoimmunity. Usually, it's not at all that simple and you need persistent research. But with the simpler models we can, so to speak, get a trace on what happens on the molecular level and what are the [biological] pathways, where either signalling is abnormal and causes disruption or one cell type is missing or does not function properly.
>
> (Researcher 5, my translation)

Thus, in some cases, the disease associations in complex diseases can be further considered with the help of other, monogenetic, diseases that are viewed to possibly share similar disease mechanisms.

Another challenge posed to GWAS studies is that "GWA study findings often account for only a limited amount of disease heritability"[197]. This has also turned some of FIMM's researchers, such as Researcher 6, back to family based association studies. Researcher 6's Group focuses on schizophrenia. Like in Researcher 5's MS research, Researcher 6's study combines the benefit of the more homogenous Finnish population base with the regional clusters in Finland where cases of schizophrenia in families are multiplied to such an extent that their study is statistically relevant.[198] However, whereas Researcher 5 sees international data comparison as a key to confirm genetic findings, Researcher 6 is focused on families with multiple cases of schizophrenia without an aim to validate the findings with international data. He explains this logic by stating that,

> There's 144 different ways you can be diagnosed with schizophrenia so even when we gather up everybody who has a schizophrenia diagnosis there could be huge amounts of heterogeneity between phenotype and therefore [there] could be huge amounts of heterogeneity as what the causal genetics are. And I think that shows as well from the heritability studies, which have shown that there's genetic component, [because] when they use twin studies looking for discordancy, they show heritability up to 80% in Finland but now when they use population based genomic methods, they show heritability is about 25% and I think that basically shows that this is the upper and lower limits of what genetic components are going to be. But I think it also shows that, if we look at populations, there's one set of genetic or genomic aspect and if you look in families, there's another genomic aspect. Which is kind of underlying my research as it is; the fact that I have stayed with family based studies rather than going into population based GWS genomic studies.
>
> (Researcher 6)

This heterogeneity of schizophrenia cases has multiple reasons, one of which is the difficulty to diagnose schizophrenia and make a clear distinction between it and other mental illnesses. Moreover, Researcher 6 notes that different families can have "different genetic causes running through them". Hence, it can make more sense to focus on families with schizophrenia without an attempt to universalise the findings. As he elaborates, when commenting on the fact that also

[197] Witte 2010, 8.

[198] Usually, it is not specified what district is studied as diseases such as schizophrenia bear a strong social stigma. However, in case of schizophrenia it is commonly known that one of the largest concentrations of schizophrenia families is in the municipality of Kuusamo in north-eastern Finland.

in schizophrenia studies there are global attempts to find genomic loci associated with the diseases,

> I'm a great big sceptic and every time I hear somebody talk about 108 loci kind of schizophrenia, I just say—I'm a fan of the *Hitchhiker's Guide to the Galaxy*—so when they say 108 is the answer I just think 'well, what was the question?'. And it's because they're using population based studies, they're answering population based questions so those 108 loci [have a] small effect but would affect everybody and I think that's going to be only a tiny proportion of what's actually going to be usable in the future. I think it's the family studies where you might actually find things which can be used; for personalised medicine, and subcategorising the disorder.
>
> (Researcher 6)

By narrowing down relevant questions when studying the disease mechanisms in family cohorts, it might be possible to clarify different types of schizophrenia. In the end, this could make the treatment also more personalised. However, Researcher 6's focus on families without international data comparison is an anomaly at FIMM, as well as in schizophrenia studies more broadly, as became clear during the interview,

> I think this is where I differ from some other people. At the moment, there's a huge trend for making sure that everything is statistically viable and replicated and you can see it in hundreds of thousands of individuals throughout the world. My own viewpoint is that because the things we're looking at could be family specific, population specific, we need to identify mutations in those families and populations and then validate them in the wet lab, to show there's functional difference some point at the cell level, at the gene-expression level.
>
> (Researcher 6)

His view that their research differs from other people can also be seen in regard to other research groups in human genomics specialisation at FIMM, as his group had little collaboration with others at the time of the interview. These challenges raised on the difficulty to use GWAS studies when examining the role of genomic loci in disease functions help to explain also a broader difference between human genomics and systems medicine research at FIMM, which also helps to explain their different kind of approach to gender differences in diseases.

3. Gender in Molecular Medicine Research

Both human genomics and systems biomedicine research at FIMM aim to benefit the future of personalised medicine by examining ways to incorporate molecular-level information into healthcare practices and drug development. The ultimate aim of FIMM's research is to aid the ways to use molecular-level information in medical decision making so that differences in patients' molecular profiles could be better taken into account. However, the two research specialisations at FIMM approach these aims from different directions: human genomics research at FIMM uses gathered population based DNA sequencing data to study genomic regions and genetic loci associated with multiple complex diseases in order to facilitate disease risk assessments and drug development. Systems biomedicine, on the other hand, is focused on identifying individual differences within types of cancers to better subgroup cancer types based on their molecular profile. This subgrouping can then help to identify disease markers that can aid cancer diagnostics and treatment.

The methodological differences also affect the ways in which gender is acknowledged in research. On the population data, gender differences are always part of clinical information of the patients whereas in systems medicine, as highlighted by Researcher 1 at the beginning of this chapter, the aim is to study cancer mechanisms by normalising other biological variations out of the data. However, a closer look into the ways in which gender differences are included into human genomics research shows that acknowledging gender differences in research does not necessarily mean that this research would help to explain the possible reasons behind them. To investigate how gender information was included into FIMM's human genomics research, and why gender differences are also relevant for systems medicine research, I will first examine what differentiates these two approaches.

3.1. Common Goals but Different Paths. Human Genomics vs. Systems Medicine

The difference between human genomics and systems medicine became clear in my interviews at FIMM. While both human genomics and systems medicine at FIMM are dedicated in further studying molecular-level differences between patients, their methodology is shaped by the different kind of data they generate and integrate into their analysis. Researcher 7 clarified the difference between FIMM's two areas,

> I would see it so that we share the same broader vision, or not the exactly same but complementing. [Systems medicine] has a different starting point. They have a more direct way to consider how single molecules affect and that way move towards personalised medicine. Let's say that they might do a lot of molecular screening with a single patient, so they gain the high-throughput approach from that whereas we have a large cohort of people, not just one patient, and we try to understand the meaning of a single variation through this cohort. So, in a way we both aim for the same outcome, but we are quite different methodologically.
>
> (Researcher 7, my translation)

The leader of FIMM, who was also a group leader of one of the systems medicine research groups, explained the difference between the research approaches in a similar way,

> They are a bit distant from one another because the [human genomics side] studies the formation of diseases and genome-level influence on that and it's based on big cohort studies on a population level. And then [systems medicine side] does cancer research. In systems medicine the genome research is research about cancer genome, not that much about individual genome.
>
> (Leader of FIMM, my translation)

Human genomics aims to identify disease linked differences from population data that could then help in disease diagnosis and treatment. Systems medicine, on the other hand, generates large amounts of data from individual patients to understand how their cancer develops in relation to drug treatment and then integrates this data to form functional analysis of cancer progression. The focus, as the leader of FIMM noted, is then on understanding cancer genome, meaning basic disease mechanisms.

A sharper evaluation of the differences between the two fields came from Researcher 1, whose work, as mentioned, was at the heart of FIMM's systems medicine research. He saw systems medicine as a necessary step towards personalised medicine,

> [The human genomics] approach is from the side of population, how to help the population and study population and then trying the associations with different diseases and from that point of view trying to locate a gene for different drug substances. But they have also noticed more and more that we cannot only think about the whole population, the Finnish population or even smaller regional populations, but we have to move more towards a stratified approach, which means that we have subgroups within population or diseases that need to be studied as their own group because that's where we will ultimately take the treatment: to the level of an individual and subgroups.
>
> (Researcher 1, my translation)

However, he also stressed that because human genomics and systems medicine share the same goal of developing personalised medicine, they might in the future become more intertwined,

> Maybe we'll meet in the middle. We cannot necessarily get to the individual level as it is very difficult to study things if we only have one patient. We can measure a lot data from one individual, in different levels: genetic data, molecular profile data, gene expression, protein expression and so on. It is difficult to study the overall structure at the individual level, but that's our aim as the individual is the one who'll receive the treatment. But it is easier to talk about things at the level of subgroups, say 10 or 20 to 100 people. In those group sizes, we start to see some similarities and we can find drug treatments for them. I'd say that we're somewhere between the individual and whole population. That's where we want to be. And that's probably where genomics and systems medicine will be combined.
>
> (Researcher 1, my translation)

This difference between the two research areas at FIMM helps to explain why gender was discussed differently by the researchers in human genomics and systems medicine at FIMM as the clinical data used in population studies always includes gender. However, if Researcher 1's prediction actualises and both human genomics and systems medicine move towards stratifying disease classifications based on patient subgroups, would gender become more relevant also for systems medicine? Could gender as a category help to stratify patient groups? To further examine this option, it is important, first, to examine how gender differences are acknowledged in human genomics research.

3.2. Gender in Human Genomics Research

The information about patients' gender is always included into the data analysed in human genomics research. Notable differences in numbers occur: in addition to obvious examples (such as breast and prostate cancer), less explicable variations occur with other diseases such as MS, migraine and schizophrenia.[199] It is important to stress that at FIMM's human genomics research gender differences are acknowledged in their GWAS analysis. As Researcher 7 pointed out, when discussing gender differences in migraine and schizophrenia, "they are both such diseases where we especially check whether there are different kinds of genetic predisposition signals between genders. We always do the sex difference analysis." Doing a sex difference analysis should not be taken for granted when talking about GWAS studies. Reedik Magi, Cecilia M. Lindgren, and Andrew P. Morris write that "despite mounting evidence for sex-specific associations with complex human traits, males and females are typically analyzed together in GWAS. In these 'sex-combined' analyses, allelic effects are often adjusted for gender if the distribution of the trait varies between males and females."[200] FIMM's research, then, is not only using data where gender is included, but actively acknowledging this difference in their analysis.

The interview with Researcher 5 illustrated well how gender differences were seen as potentially meaningful in explaining disease epidemiology but studying their origin was challenging,

> Autoimmune diseases are usually more prevalent in women than in men. There's a clear difference how much more common they are in women than in men. (…) But we haven't been able to find any genes that would explain this difference. Naturally, we speculate and the hypothesis is that it's a result of differences in hormonal functions but we haven't scientifically proven this.
>
> (Researcher 5, my translation)

[199] Clinical data shows that there are more female patients in MS and migraine statistics and more male patients in schizophrenia.
[200] Magi et al. 2010, 846.

The difficulty to explain noted gender differences was also pointed out by Researcher 7, "In migraine studies, where two out three, or more, patients are women the research is very much focused on women. Because the amount of men is so much smaller, it doesn't have as much statistical power." Thus, it can be challenging to explain gender variation with the GWAS approach.

Moreover, even if a gender specific disease associated genomic loci was located, FIMM's researchers might not study it further. When asked, what would be done if such a genetic predisposition signal was identified, Researcher 7 answered,

> it depends on the research group. From our point of view, it could be thought that we'd report the signal, explain that these and these genes have a larger effect on women and when we report it, there might be people who have just studied these genes and then realise that 'aha, there's this kind of thing' and they could start [researching it further].
>
> (Researcher 7, my translation)

When asked if they had located such gender specific genes, Researcher 7 replied, "not that I remember on the top of my head". The emphasis to study gender differences is done in accordance to the overall aims of human genomics: to identify genomic loci associated with the disease. In this case, the question is whether gender differences are connected to differences in the associations between genomic areas and the disease. If such a difference is shown, then it is reported but not necessarily further studied.

The reason for such an approach can be understood when considering how many things can influence the aetiology of the disease. As Researcher 7 said,

> if we consider, for example, migraine which is connected to menstrual periods and the point in time of the menstrual cycle you do the research; I have heard that it is clinically different. (…) That also shows how [the differences between women] can scatter. These things are so multifaceted that dissecting them is a completely different story.
>
> (Researcher 7, my translation)

His answer indicates, similarly to Researcher 5's, that gender differences can be difficult or impossible to identify as a difference in genomic loci as they can result from hormonal functions. Moreover, moving the discussion into differences *between* women in clinical data

suggests that gender difference analysis would require a different research design altogether that would take into account the circumstances in which the data has been collected. This was also highlighted in Researcher 7's answer when I asked him whether environmental factors, such as lifestyle differences, could have an influence on recorded gender differences in migraine statistics,

> Possibly yes. It goes beyond our possibilities to study the exact meaning of environmental factors [in disease emergence] because collecting that kind of data from cohort large enough is extremely difficult, expensive, and slow. When studying the genetic basis of these kinds of diseases, we need large amounts of samples. This means that we have to limit the amount of data and usually this happens by limiting the phenotype as it is difficult to monitor the fine-tuning of environmental factors. If you think of the possibility that we'd ask you what you have eaten during the past two weeks, you couldn't give an exact reply so there should be some kind of a food diary involved but also in that case you'd know that you're being monitored which might influence your eating habits. So the things linked to behaviour are not trivial.
>
> (Researcher 7, my translation)

These excerpts show the difficulties to further study the clinical data indicating gendered differences in patient cohorts. Explaining gendered differences, then, can be seen of interest for human genomics researchers at FIMM but their research is shaped according to the data available to them, which makes it difficult, if not impossible, to explain the basis of gender differences in data.

The limitations of data were also emphasised by Postdoctoral Researcher 1, whose research project tried to show the parent of origin effect (POE) from the Finnish population data. POE states that it can matter whether you inherit the genetic variation from your mother or your father as the disease phenotype is different based on from which parent you have inherited the disease linked gene.[201] It is important to note that when I interviewed Postdoctoral Researcher 1 her studies about POE were still at the early stage. Moreover, POE is still largely unstudied. There are some studies indicating POE in diabetes and BMI (Body Mass Index),[202] which is why Postdoctoral Researcher 1 also started her research as they have interconnected

[201] See for example, Kong et al. 2009.
[202] See Groop et al. 1996.

phenotypes to her research focus. Her research aims and the challenges she had faced in her research design show well the limits that one can have when studying data that has been previously collected as a part of nationwide health studies or on specific diseases.

Postdoctoral Researcher 1 had started to study the possibility of POE in dyslipidaemia, a state of having an abnormal amount of lipids in blood, causing, for example, a higher risk to develop cardiovascular diseases. She noted that POE is difficult to study because,

> the same allele, if inherited from mother, might be causal but it could not have any effect if inherited from father. So, if I have a risk allele but I know it is inherited from my father, I will not have that disease. But if it's inherited from my mother, I will know that it might cause disease. So, there's a difference between two alleles, though it'll look the same if you genotype them. We cannot differentiate these two genotypes just by genotyping. Two individuals would appear the same at their genotype level but their phenotype would be different.
>
> (Postdoctoral Researcher 1)

Another challenge arises from the need to genotype also the parents of the studied individual to verify which allele is inherited from which parent,

> Because we can only use individuals whose parents are also genotyped, unless we have their genotype we can't know which allele is coming from which parent, so that's another challenge to have that cohort. (…) [W]hen we come to family cohorts we don't have that many family cohorts with similar traits. The lipid traits we are talking about, they are not very commonly measured traits, these are very sub classified groups of measured lipid traits which are, I think, specific for this cohort [we study] and we don't find these traits in any other cohort. So it is very difficult to find the similar cohort to replicate my findings. Now we are still looking for cohorts where we can replicate our findings. So that has been really challenging.
>
> (Postdoctoral Researcher 1)

This challenge is echoed in the issues raised by Researcher 7 about the need to regulate the data gathering process and how this, then, limits the possibilities for research. These examples show why gender differences are often noted but not further studied in human genomics research, as their research would require a different sample collecting logic and, thus, would be difficult to perform with the existing data.

It is worth stressing, in addition, that human genomics' focus on disease risk assessment based on genetic information and drug development has functioned without the need to fully

explain the biological mechanism of diseases. In the KardioKompassi project, the genetic information is combined to existing FINRISK studies and calculated together with other risk factors. In drug development, the responsibility to prove a drug's safety is on the shoulders of the pharmaceutical company.[203] Therefore, while researchers strive to understand genomics of complex diseases, and possible non-genetic factors in the disease aetiology are clearly understood, their research at the moment is focused on finding genetic regions associated with the disease that could then be used in health care planning and industry.

From a gender point of view, this approach is problematical as it does not fully address possible gender differences in understanding the disease and in treating them. Still, Londa Schiebinger and Martina Schraudner have argued that rather than criticising existing research for its neglect to study gender differences, feminist scholars and gender specific analysis could be helpful when designing novel research strategies from scratch.[204] This approach has led into a formation of a new field: gender medicine. In the next part, I examine its literature considering what kinds of complications researchers face when trying to explain gender differences in clinical data. Furthermore, I will show why studying gender differences is relevant also for systems medicine research.

4. Studying Gender Differences and their Relevance in Systems Medicine Research

Gender medicine, with centres founded in major cities (New York, 2001; Stockholm, 2002; and Berlin, 2003) and textbook and journals (such as *Gender Medicine*), rose in prominence at the beginning of the 21st century.[205] As Vera Regitz-Zagrosek writes, the cornerstones of gender

[203] This assessment is based on the situation in 2014 and it is left for future research to follow whether there are differences in research design in new projects such as FinnGen.
[204] Schiebinger & Schraudner 2011 and Schiebinger 2012.
[205] Regitz-Zagrosek 2012, 1.

medicine are the clinical studies that show gendered differences "in clinical manifestation, in clinical presentation and in outcomes."[206] The active aim to develop new research designs that could account for these differences, makes gender medicine a field rather than a mere critical viewpoint. The forward-looking approach brings forth not only a promotion for the need to study gender differences but also the difficulties in addressing them in medical studies because gender differences can stem both from sex and gender differences within the studied group. What is more, in many cases sex and gender are concepts that need to be studied in unison. Therefore, to understand the problems in studying gender differences, it is important first to define these terms.

4.1. Intertwined Existence of Sex and Gender in Medical Research

In gender medicine, sex is defined as a biological difference. Gender, on the other hand, is used to indicate behavioural differences linked to societal gender roles and expectations.[207] According to Sabine Oertelt-Prigione, sex differences that are seen as strictly biological are more relevant in basic research, with animal and cell culture models, and gender analysis is required when it is important to consider whether societal gender roles have influenced observed clinical differences between women and men.[208]

Difficulty arises when considering how sex and gender are intertwined to the extent that excluding one from the research of a disease produces insufficient results. As Regitz-Zagrosek states,

> In the medical field it is not easy to separate the influence of sex and gender. On one hand, sex influences gendered medical roles, i.e. testosterone determines aggressive behavior

[206] Ibid., 3.
[207] See, for example, Holdcroft 2007, Klinge 2007, Oertelt-Prigione 2012, Regitz-Zagrosek 2012, Regitz–Zagrosek & Seeland 2012. Sex differences include, for example, hormonal differences, differences between XX and XY cells and percentage of body fat. For research focused on cell differences, see Straface et al. 2012 and Arnold et al. 2012. Regitz-Zagrosek writes also that in cellular level it is important not to see sex differences as straightforwardly dichotomous as "intersex syndromes exist as well as women and men with a hormonal or gene expression profile that is close to the other sex." (Regitz-Zagrosek 2012, 1.)
[208] Oertelt-Prigione 2012, 9.

> that may be associated with risk seeking and neglection of prevention. On the other hand, gender roles, e.g. professional exposition to stress, poor nutrition, environmental toxins, or endocrine disrupters may lead to genetic or epigenetic modifications that differ in women and men. DNA repair and epigenetic modifications are modified by sex hormone receptors. Genetic or epigenetic modifications can affect adults, but also the DNA of a developing fetus. Simpler, gender roles like exercise behavior or training will interact with sex hormones to influence physical function, for example bone density and the likelihood for osteoporosis.[209]

Viewed this way, the exclusion of behavioural differences from research even when studying cellular level differences between females and males can be difficult to justify.[210] While such differentiation could be made on studies focusing on, for example, sex differences in cell cultures, the results of such studies should be looked together with studies incorporating behavioural differences in the studied cohorts. This challenges contemporary disease study designs.

4.2. Challenges in Designing a Gender Approach in Research

Taking environmental differences into consideration in biomedical research, as was noted by Researcher 7 (see 3.2), requires time consuming and expensive data collection practices with an additional challenge of making sure that the collected information is accurate. A similar problem in gathering lifestyle information to study possible gender differences was highlighted by Researcher 3,

> When you see high mortality in males, in young males, then you start thinking about lifestyle and you start to say "they drink more" and stuff like that, like used to be true though I'm not sure if it's true anymore. So that sometimes comes up and usually the information isn't available so if you run a clinical study and you find that certain frequency of heart disease in women and then in men, it would be unusual for you to have lifestyle collected in that data. So you just see the end point. But I think that is increasingly changing so the study we are now trying to plan is a very interesting one because that would include lifestyle, that would include motion, that would include do they cycle to work, how much do they walk every day, do they walk the dog or the children and, if we

[209] Regitz-Zagrosek 2012, 2.

[210] Anita Holdcroft has also criticised the idea that gender differences would play no role in animal studies. Even if, she argues, gender is a term used exclusively to describe human behaviour, researchers should consider more how "social, environmental, and other nonbiological influences," also affect studied animal populations and, thus, can influence sex difference analysis done with animal studies. See Holdcroft 2007.

> get so far as including grocery bills it would tell you about the kind of diet they have. You know, if it's only sausages and potatoes you'd see it and if it's only salad you would see it. But we're not there yet – so most of the studies don't have that.
>
> (Researcher 3)

Researcher 3's comment on possibilities to consider sociocultural gendered differences in molecular-level analysis shows that while sociocultural information is not currently included into the research, this does not mean that it would be seen as impossible to integrate also this type of data to the research in the future.

Generating a standardised large database, incorporating behavioural information that could help to study gender differences, is difficult to do. This became clear in my interview with Eva Gerdts, a Professor of Cardiology at the University of Bergen who promotes gender medicine approaches. In our interview, I asked her about the data needed for such a research. She replied that in cardiovascular research "you need to screen all the cardiovascular risk factors because this will be the background. If you think that being depressed is a trigger, there has to be a background [to study this]." She continued,

> eventually when you have all these kind of background data then you can go in your biobank and start the analysis. But I think to really be able to put the puzzle together, you need to have a very broad collection of the different aspects. So it's typically something that would need many years to dig into and also is much more complex than something that can be done in one research group or at one university. It's typically something that had to be organised in a joint venture.
>
> (Eva Gerdts, 9.10.2017)

Reiterating the point made in 3.2, gender analysis can rarely be done if consideration for possible reasons behind gender differences has not been done when planning the research design and data gathering.

The importance for collaboration in data gathering is needed also to account for possible differences between different groups of women or men, as it is important to be able to compare

different kinds of cohorts.[211] This brings a requirement to make sure that the collected data is standardised according to common research design. As Gerdts described,

> if you want to put together data from different populations, which you'd have to do if you are into this mission, then it is also how was [the data] collected. Was the question asked the same way? People might interpret the same question in different ways and base [the answer] upon their experiences, base upon the translated wording, if you have different national translations. So it's not an easy project.
>
> (Eva Gerdts, 9.10.2017)

Understanding the challenges involved in collecting behavioural data, as explained here, is crucial in considering why there is an active need to support research initiatives that aim to generate this kind of data for research. This also helps to further grasps why gender is acknowledged but not further studied in human genomics research at FIMM.

In FIMM's population based studies gender differences are clearly visible in statistics and their relevance for research is unquestionable whereas their relevance for animal and cell culture studies has been a newer discussion. Understanding how sex and gender are intertwined in biomedical research helps to show how considering gender differences are related to systems medicine research. As FIMM's systems medicine research aims to bridge the gap between molecular-level research and clinical treatment, gender differences in clinical data were seen as relevant also for their research.

4.3. Importance of Gender Approach for Systems Medicine Research

One of the previously noted difficulties in forming gendered analysis of systems medicine research at FIMM is that, despite the collaboration between basic research and clinical treatment, gendered differences are not included into the analysis focused on cancer genomics. Nevertheless, what became clear in my interview with Researcher 2, who leads the Group D in

[211] For example, Gerdts described one study of heart failure between women who lived in East and West Germany, conducted about ten years after East and West Germany reunited. The study showed, for example, more cases of coronary artery disease with women who lived in East Germany. These differences were accounted for differences in nutrition, exercise and access to healthcare.

charge of mediating in-between clinic and basic research at FIMM, was that their research could benefit from gendered research focus.

The study of gendered differences can be seen relevant also for systems medicine research when they consider how possible treatment options would fit an individual patient. When asked whether gendered differences could play a role in disease development and the way in which patients respond to the treatment, Researcher 2 replied, "we haven't really looked into that very closely and that's very good question. That certainly it could play a role and it could play a role in how patients respond to certain kind of treatment as well. These are something, I think, [that] should be looked at more closely." Furthermore, when asked whether other studies indicate that gendered differences should be noted in the study and treatment of blood related cancers, which have been their research focuses, she responded, "Yes, I do know of one study for AML [acute myeloid leukaemia]. There are drugs being developed for this type of disease, called FLT3 inhibitors and I think they do see a slight difference in response between males and females. This [difference] is not well understood." These responses show that not only could it be interesting to study gendered differences in cancers, as these differences are not yet well understood, but also that previous research suggests that this might be a fruitful focus when developing better functioning treatment for individual patients.

When asked whether there is no possibility to currently include gender differences in research, Researcher 2 replied, "there's possibility but we just haven't had the time to look into that." This response could, and should, be analysed in terms of practical possibilities to conduct research, asking, for example, whether more funding and social attention directed towards studying gendered differences would enable and encourage institutes such as FIMM to focus their research more towards gender related questions. However, to leave the analysis at this would neglect, what I consider as, an equally important question of what kind of information

could be gained if FIMM's systems medicine research teams would focus on studying gender differences in their research.

It is important to consider what would the research team study and what could it tell about gendered differences. Consider the following dialogue we had with Researcher 2 about the possibilities to conduct gendered focus in their research:

> *Me*: If this kind of study would be done, what would it require in terms of research practices?
> *Researcher 2*: Basically, the information that we have in terms of basic information from the clinic and of course then the information we get from sequence analysis or high throughput drug testing - these could all be used to correlate, maybe, disease development to gender or also the clinical information that we receive, concerning how the patient responds to treatments. This can also be looked at and also related to gender for example.
> *Me*: Is there enough data gathered at the moment that this would be possible?
> *Researcher 2*: I would say that if you have a well developed question. For example, you're interested in drug X and you want to understand if there's a difference in response between males and females that information would be available say in the clinical registry.

The researchers in Researcher 2's Group have access to the secured clinical registry[212] that records patients' basic information, including gender, age, diagnosis and received treatment. As noted by Researcher 2, with the help of this registry, researchers would be able to follow-up possible gendered differences in disease development and treatment outcomes. Thus formed, the study would fit into the current practices of the research group with their aim to assist clinicians with molecular-level analysis. Therefore, the envisioned study would not need to fully explain the reasons behind possible gender differences.

If the researchers would want to explain why these gendered differences occur, this would require a different approach. As Researcher 2 said,

> if you want to understand the mechanism why would there be a difference between males and females, then it might require some in-depth basic research study where you'd have to setup, for example, mouse models and see if there's difference between male and female mice when they are given these drugs and then you can dig deeper into what is it in either males or females that would cause that difference, hormonal difference. So that might involve some additional laboratory setup.
>
> (Researcher 2)

[212] This registry was founded in 2010 and it is operated by the Finnish Haematology Association. Signed confirmation from the patients is required before the data is included into the registry. More information can be found from <http://www.hematology.fi/en/book/export/html/5169> [Accessed 17.4.2017]

This comment is interesting for two reasons. First, it highlights how different research questions might require different research settings. This is important to emphasise as it shows the connection between meanings assigned to gender in relation to cancer research and possibilities to use gendered focus in benefitting medical practices. If the research is focused on pointing out to clinicians that it makes better sense to assign certain kind of therapy based on patient's gender, then it can be enough to combine sequence analysis and drug screening results with the available patient data from the clinical registry. In case the research aims to understand why there is a gendered difference in patients' response to treatment, then a different laboratory setting, based on animal experimentation, would be planned. This study would then be focused on explaining the connection between sex and drug response in the studied disease type. Secondly, researcher 2's answer shows that the basis for this gendered difference in haematological cancers is assumed to be a sex difference—a *hormonal* difference that can be studied with animal models.

The assumption that relates differences in the drug response in connection to sex hormone differences sets the assumed requirements for further exposing and studying this difference. At the end of our interview, we resumed the discussion on the importance on studying gender differences. At this point Researcher 2 mentioned that, if the study would aim to examine whether there is sex difference in drug sensitivity, it would not require any changes into the sample gathering process as the hormonal differences could be studied from patients' blood samples. It is not surprising that Researcher 2 connects the possible gender difference in drug response to hormones. The focus on differences in drug effects based on hormones is a topic that has gained increasing notice within the medical community as Spoletini et al. highlight in their article "Sex Differences in Drug Effects: Interaction with Sex Hormones in Adult Life,"

(2012) "the available evidence suggests that sex hormones influence drug absorption, distribution, metabolism, pharmacodynamics, and adverse effects."[213] Furthermore,

> in women the phase of the menstrual cycle, the phases of reproductive life (i.e., pregnancy, menopause, etc.), and fluctuations in concentrations of sexual steroids further influence both pharmacokinetics and pharmacodynamics. Furthermore, the different hormonal milieu, the use of oral contraceptives or hormonal replacement therapy, the sex hormone-related changes in total body water or in the amount of fat, all influence the overall effect of drugs.[214]

Thus, hormones are not only shown to influence drugs' efficiency but they are also linked with considerable differences between female and male patients. Researcher 2's focus on hormonal differences as the basis for possible gender differences in cancer treatment can be understood in the light of this research. Hence, the first step in examining the mechanism behind gendered differences would be directed according to the hormone based hypothesis and functional analysis could be performed with animal models.

It is important to note here how the study is framed according to an already existing view on sex differences in drug responses. At the moment, systems medicine researchers at FIMM could create functional animal models based on drug effect data, which then differentiates systems medicine from human genomics, where gender differences are difficult, if not impossible, to study with existing data. Yet, the differentiation is then based on the assumption that only sex differences are relevant for FIMM's systems medicine research, which excludes the possibility to consider possible gender differences in relation to their research. What if, following gender medicine, a noted gender difference in studied disease is not based on hormonal differences or hormonal differences would not fully explain noted differences in patients? This is a relevant question, especially if FIMM's systems medicine research would move towards developing predictive models of drug responses, or if environmental factors

[213] Spoletini et al. 2012, 92.
[214] Ibid., 93.

would have an influence on drug responses.[215] Here, systems medicine research shares the challenges with human genomics research as explaining possible gendered sociocultural differences requires a different kind of data.

In this chapter, I have argued that when considering how the category of gender was acknowledged in FIMM's research, it is necessary to question researchers' possibilities to explain the basis of noted gender differences. Seen this way, the difference between human genomics research and systems medicine appears very different from my initial stance, which emphasised how gender differences were included into human genomics but not to systems medicine research. Because both human genomics and systems medicine aim to advance personalised medicine, understanding possible gender differences in disease emergence and treatment outcomes is relevant for both fields. While human genomics researchers at the present state always acknowledge possible gender differences, they seldom explain the reasons behind such differences. One reason for this has to do with the existing data. I pointed out that studying gender differences is challenging because it requires researchers to consider both biological and behavioural differences. As behavioural data is difficult, time-consuming and expensive to collect, such information is often left outside of research. In systems medicine research, due to its focus on drug effect analysis, sex difference analysis can be more easily implemented in their existing research approaches by including animal models to their research. However, if their research would move towards developing preventative healthcare strategies, or if environmental factors would influence drug treatment results, it would be necessary to consider also environmental factors in their analysis. Therefore, when considering the possibilities to study both sex and gender differences in diseases, both human genomics and systems medicine

[215] FIMM's scientific advisory board has, in their 2015 report, recommended FIMM's systems medicine research to consider possibilities for developing preventative drug response models. The report can be read from: <<https://www.fimm.fi/sites/default/files/Fimm%20report%202015.pdf>> [Accessed 5.4.2018]

share the same challenge to obtain suitable data for such analysis. In Chapter 4, I will discuss in more detail why environmental data is important also for the future development of systems medicine research. In order to make that analysis, however, I will first need to offer a fuller explanation of how systems medicine research is conducted at FIMM and how it uses systems biology approach in biomedical research. The next chapter will offer a more detailed description of systems medicine research at FIMM.

Chapter 3

Managing Individual Variation

From Systems Biology to Systems Medicine

During my fieldwork at FIMM in 2014, I soon realised that the term "systems medicine" is far from self-evident. Below are some answers I received when I asked my interviewees how their research is connected to systems medicine:

> Researcher 13 (Group A): [Systems medicine] means that I don't study just one gene based on one hypothesis, as if that would be the most important thing in the world. Instead, with the use of high-throughput screening technology, I can systematically watch all the genes, or [the effect of] cancer drugs as we do here. Thus, I can, without any hypotheses, see what the result is. That is why I'm now spending a lot of time with our bioinformaticians here, because of course you should, then, find the pattern from the data. And for that you need mathematics, statistics and informatics. (My translation)

> Researcher 17 (Group E): How do you understand systems medicine? Does it refer to the fact that there's a lot of data? Because this is always as unclear for me so I was wondering how you understand it. (My translation)

> Researcher 11 (Group H): I don't really know the term systems medicine. I don't quite understand what it is.

As stated in brackets, these researchers work in different groups. However, all these groups were listed under "systems biomedicine" specialisation at FIMM when the interviews were conducted.[216] Thus, these excerpts portray the variety of responses I received when asking FIMM's researchers, whose research is categorised under systems biomedicine specialisation, about their link to systems medicine. The response of Researcher 13 suggests a clearly defined understanding of her work's relation to systems medicine. To the contrary, Researcher 17 and Researcher 11, who is also a leader of Group H, replied to my question in a way that shows a hesitance towards the term "systems medicine".

[216] Group H is no longer at FIMM.

The hesitance towards the term suggests that a substantial consideration of the meaning of systems medicine is needed. In the previous chapter, I highlighted how human genomics and systems medicine at FIMM differ in the way in which they include, and omit, gender differences in their research. The analysis, then, proceeded to explain how human genomics and systems medicine research differ in their approach to develop personalised medicine: human genomics research at FIMM uses population based large data sets to study genomic regions and genetic loci associated with multiple complex diseases, such as diabetes, cardiovascular diseases, and schizophrenia, and also uses gathered DNA sequencing data to facilitate disease risk assessments and drug development. Systems medicine, on the other hand, is focused on identifying individual differences within types of cancers to better treat patients and identify subgroups within cancer types based on their molecular profiles. This subgrouping can then help to identify disease markers that can aid cancer diagnostics and treatment. The difference between human genomics and systems medicine research, based on comparisons made by Researcher 1 and FIMM's leader, offered a somewhat clear picture of systems medicine research at FIMM. This is no surprise, as both Researcher 1 and the leader of FIMM play a substantial role in FIMM's grand challenge: individualised systems medicine (ISM) in cancer.[217] This grand challenge is a research goal for 2020 that helps "to focus strongly on grand challenges in the society, and to make almost the entire institute to work together towards such goals."[218]

While the ISM project is the cornerstone of FIMM's systems medicine research, examining it is not enough when describing systems medicine specialisation at FIMM. The ISM project, which started with a pilot project on acute myeloid leukaemia (AML), aims to aid the

[217] In 2014, FIMM had two grand challenges, following the two specialisations of the institute: ISM for systems biomedicine research and "Finnish genomes empowering personalised and predictive health" for human genomics research area. Currently the number of these challenges in three, as a new challenge, "digital molecular medicine", has been added after my fieldwork.
[218] See: < https://www.fimm.fi/en/research/grand-challenge-programmes> [Accessed 12.12.2017].

development of personalised treatment options for cancer patients. In 2014, the project had spread to studying other haematological cancers as well as some solid tumour cancers. As highlighted in the definition of grand challenge projects, they bring almost the whole institute to work together. However, the ISM project does not require active participation from all the research groups under systems biomedicine at FIMM. Of the eight groups working under systems biomedicine label in 2014, only four had active participation in the ISM project. Thus, the differences in above interview excerpts can be partly explained by the fact that Group A was closely linked to the ISM project whereas Groups E and H were not. To complicate the picture further, researchers within each group have their own research projects. This means that even in Groups A, B, C and D, that were involved in the ISM project, all members of the group did not work in the same project. Furthermore, research collaborations surpassed group limits in multiple different projects that were more linked to external funding opportunities than institutional strategies. Thus, making clear distinctions between groups is counterproductive when describing how systems medicine research groups functioned at FIMM.

How can the practices involved in systems medicine research be described when even the term itself was unclear to some of the researchers? In my research, I have followed Bruno Latour's suggestion, presented in his book *Reassembling the Social* (2005), that social scientists should always first let the actors themselves to define what they do, even if it does not fit into their expectations of the groups that these actors are part of.[219] Thus, I have approached these seeming contradictions as a fruitful starting point rather than a hindrance to the definitional clarity. Therefore, instead of only focusing on FIMM's ISM program to explain systems medicine research in practice, I have mapped how FIMM's systems biomedicine specialisation has been formed in accordance to both institutional research strategy (highlighting novel approaches in cancer research) and external funding possibilities (highlighting personalised

[219] Latour 2005, 23.

medicine initiatives). This has led me to consider the systems medicine approach as something which is not only influencing particular research projects, termed as "systems medicine research", but as something which represents broader changes happening in the biomedical research—highlighting the need for its clinical relevance. This has influenced the ways in which models used in medical research are developed in institutes such as FIMM. This clarification is essential when analysing the social context of systems medicine research and its connection to the broader aims described in the personalised medicine initiatives. Hence, before asking how FIMM's systems medicine research is connected to the broader goals of personalised medicine,[220] I will describe how FIMM's systems medicine research operates in practice.

I will start my analysis by considering how a systems biology approach was implemented in FIMM's ISM project. I will explain how the focus on drug sensitivities and resistance has formed a pragmatic focus for the ISM project and moved it from systems biology to systems medicine research. This focus is balancing immediate clinical applicability of research and a more basic examination of disease mechanisms. Both of these aspects help to define what the systems medicine research means in relation to the ISM project. The second part of this chapter focuses on the methodological challenges emerging when systems biology moves towards systems medicine. In accordance with Annamaria Carusi's work on systems medicine,[221] new challenges for model validation result from the requirement for medical relevance as it needs to account for variations between patients. Model validation in systems medicine research requires consideration of how different models can inform one another as well as social considerations on how to form interdisciplinary collaboration between researchers from very different disciplinary backgrounds. The third part of the chapter moves on to discuss how FIMM as an institute has actively tried to support interdisciplinary and innovative research. These considerations are important in order to show how the ISM program is enabled in practice

[220] I will return to this question in Chapter 4.
[221] See Carusi 2014.

and to question broader changes that systems approaches can bring to medical research. The final part of this chapter deepens this point by complicating the view of systems medicine research as a clearly defined field. Thus, rather than seeing systems medicine as a well-defined approach in medical research, a more fruitful way to discuss the changes brought by systems approaches is to consider how the relevance of medical research is more and more tied into the question of contextual interactions in disease models. This view helps to see how a systems approach can influence medical research, and its link to the clinic, more broadly by forming new questions about the relatability of different kinds of models when thinking of the possibilities to model the complex interactions in human bodies.

1. Individualised Systems Medicine in Cancer

One of the most visible sides of FIMM's ISM grand challenge has been the pilot study on acute myeloid leukaemia (AML), which started in 2010 when Group D was formed. Group D has a central role in FIMM's systems medicine research as it functions as a mediator between the haematology clinic, situated in another building in the same hospital district, and FIMM's researchers. This role includes gathering and processing patient-derived cancer samples that are then analysed by FIMM's researchers. Part of the sample is also stored in the haematology biobank specialised in blood related diseases, hosted by FIMM and organised together with the Finnish haematology association and the blood service of Finnish Red Cross. These patient-derived *ex vivo*[222] samples form the basis for FIMM's AML pilot project.

As written on the ISM webpage, the AML pilot study aims to aid development of individualised treatment options for AML patients, who "desperately need new therapeutic

[222] As translated, "out of the living".

options to replace the 30-50 year-old chemotherapeutic regimens."[223] In addition to the need to create new treatment options, AML was chosen because it is a haematological cancer. This means that it is relatively easy to acquire patient samples to analyse and follow-up the progress of individual AML patients. As the leader of FIMM commented on the selection of AML,

> When we talk about leukaemia, it is easy to take samples of the whole body. The solid tumours, on the other hand, grow in a particular organ. If they are in the internal organs, you cannot take a sample from there in a similar way. It's different with the bone marrow: even if it doesn't sound like a nice procedure, taking a sample from there is still a normal clinical practice. (…) It's not dangerous, it's not overly complicated or difficult and all haematology patients are used to having their bone marrow samples taken.
>
> (Leader of FIMM, my translation)

When patient samples are collected from the clinic and processed by FIMM's personnel to isolate mononuclear cells (which contain DNA), they can be used for DNA, RNA and protein sequencing to form a personal molecular profile. The samples can also be put through the drug sensitivity and resistance testing (DSRT) platform to study how patient-derived cancer cells react to over 300 different drugs in different concentrations and combinations.[224] Integrating the data generated by the DSRT assay with the data gained from molecular profiling and clinical database can then help both in planning individualised treatment options as well as in studying basic disease mechanisms. Comparisons between individual cases can also help to define subtypes within studied cancers.

In what follows, I will first examine the basis for a systems biology approach in cancer research by examining the complexity connected to cancer biology and how technological developments are seen to help to analyse this complexity. I will then move to consider how FIMM's research has moved from systems biology to systems medicine as the patient-derived *ex vivo* samples and the DSRT platform form the pragmatic clinical relevance for the program.

[223] <<https://www.fimm.fi/en/research/grand-challenge-programmes/individualized-systems-medicine-cancer>> [Accessed 15.12.2017]

[224] At the beginning of the project, this number was less than 200, in 2014 it was over 300 and currently the number of studied drug chemicals is over 500.

Finally, I will show how DSRT also offers novel possibilities to study broader patterns in cancer disease mechanisms, thus making it possible to identify cancer subtypes.

1.1. Systems Biology and Cancer Research

Trying to cope with the multiple ways in which cancers emerge and develop in human bodies has always been part of cancer research and treatment. While more is understood about the possible mechanisms of how cancers develop within the body, the biological complexity of cancer and the heterogeneity of cancer patients makes their treatment challenging. The goal of curing cancer seems still distant and, thus, many researchers have focused on developing prevention and early diagnostic methods as a way to prevent the forming of cancerous cells or removing cancerous tissue before cancer becomes unmanageable.[225] Still, to manage such preventative actions requires a better understanding of basic cancer mechanisms, which are difficult to formulate due to the biological complexity and heterogeneity of cancer types.

Cancer is a disease caused by abnormal cell function that leads cells to grow and avoid normal programmed cell death (apoptosis), replicate limitlessly, form new blood vessels and invade other tissues and, in some cases, travel to other parts of the body to form new tumours (metastasis).[226] While this definition highlights the centrality of cell malfunction in the cancer definition, it contains numerous cancer types ranging from solid tumour cancers such as breast and lung cancer, to haematological cancers with no solid tumours. Moreover, even within one

[225] Hendrickson 2011.

[226] These characters are usually mentioned as ”six essential alterations” that are linked to the process in which normal cells turn cancerous and form tumours. They were developed by William Hahn & Robert Weinberg in their paper “Modelling the molecular circuity of cancer” published in the *Nature Reviews Cancer* in 2002. These six alterations are:

1. Self-sufficiency in growth signals
2. Insensitivity to growth-inhibitory (antigrowth) signals
3. Evasion of programmed cell death (apoptosis)
4. Limitless replicate potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis

See Hahn & Weinberg 2002. In addition, Marcus & Cesario note that there has been proposed seventh needed alteration, that of cancer-related inflammation. See Marcus & Cesario 2011, 4.

type of cancer there can be multiple subtypes. For example, breast cancer has different subtypes based on the origins of the tumour (either in lobes or ducts leading to the mammary glands in breast or in tissue surrounding the ducts and lobes) and whether the tumour is contained within the walls of ducts or lobes or has invaded to the outside breast tissue (making it possible for cancer to spread to the other parts of the body). In addition to this differentiation of breast cancer types, which is based on the analysis of cancer cells under microscope, breast cancer cells can be also analysed based on their molecular characteristics.[227] This analysis is done in order to classify whether the tumour is likely to grow and what kind of treatment would be the most effective. This molecular characterisation of breast cancer is often divided into three subtypes: Luminal, HER2 and Basal (triple-negative).[228] Both cellular and molecular-level analysis are important in order to decide whether and how surgery should be performed and what kind of treatment should be assigned for the patient. This example highlights that while all these subtypes fall under the classification of breast cancer, their further identification is crucial to make the prognosis and treatment as exact as possible.

In order to account for differences in molecular profiles, the focus in biomedical research has started to shift from the study of distinct genes towards understanding how the cells operate. As Kevin Strange points out, the last half of the 20th century biological research focused on revealing functional properties of individual entities, such as genes. While Strange notes that this kind of 'reductionist' approach is often needed in biological research to manage the studies, a problem arises with the 'naïve reductionism', in other words an assumption that this kind of knowledge would be sufficient when explaining functions of a biological system. As Strange puts, "organisms are clearly much more than the sum of their parts, and the behavior of complex

[227] For the description of the heterogeneity of histologic breast cancer types, see Li et al. 2005.
[228] See Schnitt 2010 for more elaborative description of differences between these molecular subtypes.

physiological processes cannot be understood simply by knowing how the parts work in isolation."[229]

As Marta Bertolaso, whose work has focused on philosophy of cancer, states, cancer research fell under this 'naïve reductionism' for decades but increasing understanding of the complexity of cancer biology has directed the research towards systems biology approaches.[230] As has been highlighted in Chapter 1, systems biology approaches aim to account for the complex interactions within the cells, and between them, by studying these functions as systems of networks. In cancer studies, it is important, for example, to take into consideration the signalling pathways of molecules within and between the cell(s) that control cell functions, such as cell death, which are the basis for the emergence and operations of cancerous cells. Thus, the focus has shifted from studying disease linked genes to asking how these genes operate in an interaction within the cell, and considering also how cells receive external signals that can influence these interactions. Therefore, studying molecular interactions in systems biology requires DNA, RNA as well as protein data to map out how cell malfunctions emerge and develop.[231]

While the term "systems biology" functions as an umbrella term to discuss new systems approaches in biological research, in FIMM's cancer research it refers mainly to possibilities linked to big data. As Researcher 1, the principal investigator of Group B focused on developing computational systems medicine models, remarked "for me, [systems biology] refers mainly to modelling big data, integrating it. Modelling genetic, molecular biology, data." Due to the complexity of studied systems, a systems biology approach requires a lot of data to produce functional models of disease mechanisms. Thus, systems biology is based on new technologies that enable researchers to generate and process large datasets that can be used in modelling

[229] Strange 2005, 968.
[230] Bertolaso 2009, 80.
[231] See Bertolaso 2016 for a comprehensive account of changes and challenges in recent cancer research from a philosophical perspective.

complex network interactions within the cell. In our interview, Researcher 1 explained the importance of these technologies by comparing them with earlier modelling options,

> In the traditional modelling, there are few variables. Let's say, for example, blood pressure or cholesterol levels. In the models based on differential equations, you cannot have more than ten variables because we cannot make a model, or at least we're unable to analyse it reliably, if there are too many variables. When we go to systems biology (…) there we aim to model the functions of all the human genes. According to the current knowledge, there exists over 20,000 genes, over 100,000 proteins. Thus, the number of genetic variables, that we can currently measure, is several millions. There you are faced with the limits of traditional modelling with which you can only have less than ten variables.
>
> (Researcher 1, my translation)

Systems biology depends on developing new computational and mathematical tools to generate and integrate data because of the large amount of data required for modelling biological systems in a way that does not reduce the complexity of biological interactions. Thus, systems biology is often defined as a big data approach to biology. As stated by Karen Kastenhofer, the concept of systems biology is so intertwined with the technological ability to process information that "when looking at its cultural traits, systems biology is *firstly* characterized as a contemporary Big Science endeavour and only *secondly* as relating to a molecular biology tradition."[232] From this perspective, systems biology seems to be more connected to the technological possibilities it suggests than to a specific method in molecular biology.

However, central in Researcher 1's definition of systems biology—referring "mainly to modelling big data, integrating it. Modelling genetic, molecular biology, data."—is the importance of *integrating* big data in the models. Researcher 1's definition of the term follows a widely accepted view of systems biology as an approach that aims "to understand how individual proteins, metabolites, and genes contribute quantitatively to the phenotypic response."[233] In other words, while systems biology is based on quantitative approaches, where

[232] Kastenhofer 2017, 159.
[233] Gu & Sauro 2014, 134.

large amount of data functions as the basis for models, its aim is also connected to producing meaningful integration of different kinds of data into functional models. In this regard, it follows the broader goals of molecular biology research: trying to understand how organisms' genotype and phenotype are functionally linked.[234] In other words, computational simulations in systems biology research aim to model the functions within the cell to understand the background of phenotypic differences. How to integrate different kinds of data into a functional *in silico*[235] computer simulation model is one of the key methodological questions in systems biology research. This question is also the point in which FIMM's research takes a step away from systems biology's general aim to model biological systems and moves towards the systems medicine approach.

1.2. From Systems Biology to Systems Medicine

Cancer can emerge and develop differently in individual patients. As the example of various molecular subtypes in breast cancer shows, even within one cancer type the molecular profiles of cancer patients can vary greatly. As Annamaria Carusi has emphasised, this means that systems medicine research differs from systems biology because, in order to produce clinically relevant disease models, it must consider variation between individual patients.[236] Thus, FIMM's ISM project, aiming to develop individualised treatment options, faces a challenge of how to consider the genetic profile of each patient when defining and treating cancer. The heterogeneity of molecular differences between cancer patients is forcing the researchers to consider how, and to what extent, the particularity of every cancer case can, and needs to, be

[234] 'Genotype' refers to person's molecular characteristics, 'phenotype' to observable characters of the body. In cancer research this distinction could be viewed, for example, as a difference in defining the locus and extent of a tumour (phenotype) and molecular profiling of a cancer subtype (genotype).
[235] As translated, "in silicon", referring to the material used in computer chips used to store large amounts of data.
[236] Carusi 2014. See also Wolkenhauer et al. 2013.

taken into account in cancer research and treatment. This question has lead institutes such as FIMM to develop new research approaches.

FIMM's ISM project has approached this challenge by focusing on modelling drug functions. As the Leader of FIMM explains,

> It is impossible to model perfectly what happens when something goes wrong somewhere. We need to take a bit more pragmatic approach. An example of a pragmatic approach is that when in a typical research project, or in a "researcher's mid-set", you'd try to create a perfect model of cancer's biological signalling and try to understand it, we, instead, start immediately to test how different drugs work [in cancer samples] and model that drug effect. We don't try to model all the background biology, because it is very challenging, but we focus on examining how the drugs affect (…) Our systems biology thinking has, in a way, moved from understanding genomics and cancer biology to understanding and testing drug-effects and modelling their clinical use. And when we added the clinical evidence, we acquired a clinical viewpoint. That is why we have started to call it systems medicine, not systems biology. (…) So we have systems biology principles there but maybe a bit more realistic viewpoint in that we see that the most important thing now is to understand the drug effects, find the best [drug] combinations and that we cannot control all the signalling pathways at the moment.
>
> (Leader of FIMM, my translation)

As this statement shows, there are two reasons why FIMM's systems medicine research has been focused on the drug effect analysis. Firstly, it is viewed as a pragmatic approach as the focus on drug effects in cancer samples means that FIMM's researchers do not need to model all the interactions within the cancer cells but only those connected to the effects of the drugs. Secondly, it is seen as a clinical approach as the drug effect analysis can be brought back to the collaborating clinicians that can use this information when planning treatment options. How this operates in practice has been described in FIMM's first publications of their AML pilot study under ISM program.

As the article written by Pemovska et al. describes, FIMM's AML pilot study procedure contained four stages.[237] Firstly, the *ex vivo* cancer cells samples, acquired from 18 patients, were tested with the DSRT platform. The DSRT platform, in this study, consisted of 187 drugs that had not been used for AML treatment, containing both approved drugs used for other

[237] See Pemovska et al. 2013.

diseases as well as interesting preclinical drugs. To gain comparative perspective, the cancer cell samples were also tested for chemotherapeutics currently used in the treatment of AML patients to see whether other drugs would offer a better response. Secondly, they evaluated drug sensitivity responses both in cancer cell samples and in the control samples consisting of normal bone marrow cells. Thirdly, based on the drug efficiency results, some patients were prescribed suggested off-label drugs (meaning those drugs that were already in clinical use but for other diseases), which enabled researchers to verify whether DSRT-based predictions were functioning *in vivo*. Fourthly, by following patients' cancer progression by taking and analysing samples from relapsed patients, they were able to analyse "the molecular mechanisms underlying development of cancer progression and drug resistance."[238]

This description of the AML pilot project highlights two different aspects of the ISM grand challenge: (a) producing research that can offer clinically usable treatment predictions based on the molecular information and (b) to form better understanding of cancer subtypes by analysing differences and similarities in patients' molecular profiles. The clinical relevance of the AML pilot is clear in this procedure, as the DSRT results were brought into clinical decision making with eight patients who had already undergone and become resistant to existing chemotherapy treatment options.[239] These eight patients were all prescribed different combinations of off-label drugs, and three of them had a response to the treatment. Even though other treated patients did not fulfil the response criteria set by European LeukemiaNet, all eight patients were re-sampled and re-analysed to form "a real-time continuous cycle of learning and optimization of therapies, one patient at a time, thereby creating an individualized systems medicine process for improving cancer care."[240] As this statement shows, the clinical evidence, as noted by the Leader of FIMM, was the basis for FIMM's systems medicine approach as it

[238] Ibid., 1417. *In vivo* translates as "within the living".
[239] Ibid., 1418.
[240] Ibid.

enabled researchers to verify DSRT-based treatment predictions and fine tune the procedure accordingly. However, the second emphasis of the ISM project, the identification of sub categories, was seen as a key factor in developing future cancer treatments.

While the DSRT platform could, as explained, provide individualised drug sensitivity predictions, it is important to see how the efficiency of these predictions, as well as the DSRT platform's possible influence on the studies of cancer mechanisms, was based on its usefulness in identifying subcategories within cancer types. In order to understand how the DSRT platform can aid in the subcategorising of cancer types, it is important, firstly, to ask why certain drugs were included into the DSRT platform? Secondly, how was patients' molecular profile connected with the DSRT results to provide individual treatment suggestions? The answers to these questions will help to explain why the individual treatment suggestions and future goals of the ISM project are linked to the need to subcategorise diseases.

The drugs included in the DSRT platform were carefully chosen. This became clear in my interviews with Researcher 8, who leads Group C focusing on modelling chemical systems in cancer and who has been one of the main people developing the DSRT platform.[241] He told me that the drugs included into the first AML's study's DSRT assay were selected together with the clinicians collaborating in the project. The aim, he explained, with clinically approved drugs was to select those used in other cancers, because it would be easier to justify off-label use of another oncology drugs when treating AML patients. In regards to preclinical drugs, they tried to select chemicals with structures conducive to offering a good drug-response to some AML subtypes. Thus, the selection of drugs already required a consideration towards known molecular differences in AML. As mentioned at the beginning of their 2013 publication, prior studies had divided AML patients into eight different subtypes and the genomic changes in

[241] I conducted two interviews with Researcher 8, one in 2014 and one in 2017. The follow-up interview in 2017 focused on the DSRT platform and FIMM's pharmaceutical collaboration, which I will analyse in more detail in Chapter 4.

AML were already relatively well understood.[242] While these known genomic changes suggested multiple possible driver genes that could be targeted in drug treatment, FIMM's researchers emphasise that the "genetic testing of patients with AML has yet to result in effective personalized or stratified therapies."[243] In other words, DSRT was formed to aid possibilities to use molecular-level understanding of AML subgroups in patient care.

However, this does not mean that the patient samples would have been straightaway categorised according to the prior subgroup divisions in the FIMM's AML study. Instead, the prior studies functioned as a way to justify the need for developing the DSRT platform as well as helping in the first stage drug selection.[244] In the actual study, patient samples were divided into subcategories only at the second stage of the procedure. The stratification of patient samples into subgroups was done in regards to their drug sensitivities. As Pemovska et al. write, "despite the underlying genomic and phenotypic variability in AML, similar drug sensitivity patterns were observed among the AML patient samples for certain drug classes"[245] Hence, the known molecular profiles of the included drugs, rather than that of the patient samples, functioned as the basis for patient samples classification.

Thus, while the molecular profiling of patient samples was an essential part of the AML study, its role was to help to explain drug effects rather than function as a basis to sign drugs to the patients. This clarification is needed to understand that although molecular-level information already exists of AML, at the moment it is not filtered enough to be used in defining functional drug-patient interaction predictions. The hope with the DSRT led studies, then, is to use the knowledge of drugs and preclinical chemicals in defining patient subgroups that would respond to the molecularly targeted drugs. This comparative approach can, then, help to

[242] Pemovska et al. 2013, 1417.
[243] Ibid.
[244] As Researcher 8 pointed out, the DSRT platform could be modified also according to the DSRT results in the future studies.
[245] Pemovska et al. 2013, 1420.

evaluate whether DSRT results for an individual patient are reliable. As Researcher 8 pointed out, it is necessary to try to identify molecular mechanisms forming cancer subgroups and not only use DSRT to gain patient specific data as,

> it may look promising but you don't know for sure was this really something that matters or was it just by chance that we stumbled upon this, did we look at the right things? But to test it you need to ultimately to do it more systematically, that you start looking for a certain pattern and then go back and test that in more than one person. And then you know how strong the link is (…) how many you'll have to test to give a sense whether it works or not. So that's what we've been aiming for.
>
> (Researcher 8)

In other words, the comparative analysis, that forms the basis for cancer subgroups, is needed to ever gain enough relevant data to convincingly model the effects of drugs. In so doing, this subcategorisation simultaneously offers more information about functional molecular-level differences between these subgroups. This dual approach in FIMM's systems medicine research forms a requirement for two kinds of ways in which big data approaches are used in their research.

1.3. Big Data in Systems Medicine Research

While FIMM's ISM project is defined as an individualised approach to medical research, the development of personalised treatment options is based on a comparative approach between multiple patients. As the Leader of FIMM reminded,

> Individuals [taking part in the studies] form a series of patient data (…) now we have started to see kinds of general laws that recur from patient to patient and through this we can then find larger groups and generalisations that could benefit cancer treatments more broadly. (…) So, even if it is called "individualised systems medicine", the collection of scientific information has to be based on larger data sets.
>
> (Leader of FIMM, my translation)

The aim of finding general laws of biological systems is a key element in systems biology research. As mentioned, this requires a lot of data. Here, the challenge raising from the systems biology approach is how to meaningfully integrate different kinds of data when simulating the drug effects with *in silico* models.

The big data approach in the AML study refers to the ways in which different kinds of data from different sources are integrated together to form an *in silico* predictive model of drugs' functions in relation to cancerous cells. In the previous section, I have shown how the focus on drug effects has helped FIMM's researchers to stratify heterogeneous patient profiles by categorising them based on their drug sensitivity and, then, modelling different functional possibilities behind such sensitivities in accordance to the chemical structure of drugs. In the AML pilot project, the robot assisted high-throughput technology in the form of the DSRT platform, molecular profiling, and clinical database were used to generate large amounts of data to predict individual drug effects. This data was then integrated into predictive models that could be used to evaluate which drugs would possibly target individual patients' disease profile.

By dividing patients into subtypes according to the drug effect, FIMM's research also gives insight into which drugs could work with which cancer subgroups. This information is especially important with the chemicals still in their preclinical phase, in other words, that are not yet established as clinically used drugs. While FIMM does not itself organise clinical trials, its research can help pharmaceutical companies to focus on promising molecularly targeted drugs and suggest with which patient subgroup it should be tested in a clinical trial.[246]

The DSRT platform offers an invaluable addition to subcategorisation of patient groups as it helps to filter the existing available data of possible cancer subgroup biomarkers, meaning measurable biological entities that can be used to identify the subgroup, and their link to the drug sensitivities. There exist multiple studies on possible driver genes, in other words gene mutations that are central in the operation of cancerous cells, on different cancer types. These studies are often based on publicly accessible large datasets on, for example, gene expression data of cancer types.[247] As mentioned in relation to FIMM's AML study, such studies have also

[246] I will analyse FIMM's collaboration with pharmaceutical companies more in Chapter 4.

[247] In the previous chapter, I mentioned how FIMM's researchers in the human genomics side were dedicated in establishing SISu, an open access database of DNA sequences gathered in Finnish clinical studies over decades. As can be seen in this chapter, these kinds of DNA sequence databases, based on particular diseases, are seen

been used to categorise cancer subtypes. However, when I spoke with Researcher 12, who worked in Group B and whose work focused on drug sensitivity predictive models, he highlighted that it was essential to generate functional data of drug effects to analyse what information in a vast number of studies made of cancer biomarkers and driver gene mutations was usable in drug therapies. As he pointed out, with large datasets, you will have a lot of "noise", that is to say, mutations that are real but not relevant when understanding the mechanisms of studied diseases. Furthermore, even though some driver genes could be central for the operations of cancerous cells, they might not be "druggable" molecular targets. In such cases, gaining functional understanding of the operation of signalling pathways linked to the functions of such driver mutations is essential in order to locate possible drug targets "upstream" in the pathway. As noted by Researcher 12, targeting this part of the signalling pathway would then also influence the actions of the driver gene. Hence, the value brought by the DSRT platform is connected to the ability to generate data that can be used in functional models of the signalling pathways which will then help to filter existing molecular profile data.

Seen this way, there are two ways in which big data is essential for FIMM's ISM studies. Firstly, it forms a basis for the DSRT platform through forming hypotheses of the possible driver mutations and cancer biomarkers. These hypotheses are based on available databases and known biological signalling pathways. These studies can then form generalised models of the cancer biological systems which can be used to model possible drug resistances. As stated by

central for establishing a basis for further studies because they form a basis for big data approaches. For such cancer databases, see for example, The Cancer Genomic Atlas: <https://cancergenome.nih.gov/> [Accessed 21.12.2017]. The value seen in big data approaches in forming predictive *in silico* models is evident in the many possibilities to participate in international "dream challenges". Many researchers at FIMM, especially PhD students, mentioned possibilities to participate in these "dream challenges" where participants are provided with anonymised clinical data acquired, for example, from clinical trials but without the result of the trials. The participants have to, then, submit their suggestions for best possible predictive models based on this data, which organisers of the competition can then compare with the actual results of the trial. The winning models in these competitions can sometimes even provide the basis for future predictive models. FIMM's researchers, especially PhD students, specialising in *in silico* modelling have taken part in these kinds of challenges and, for example, in 2015 won a Prostate Cancer Dream Challenge, see: <https://www.fimm.fi/en/news/1440704795> [Accessed 21.12.2017].

Researcher 12, this kind of research produces a lot of possible molecular drug targets. Thus, secondly, to gain clinically relevant predictive models, FIMM's ISM project is invested in integrating data generated from patient-derived cancer cell samples. As emphasised by Research 1 (see section 2.1), this approach requires the tools used in systems biology research in order to meaningfully integrate vast amount of different kinds of data. The connection to clinic also makes it possible to verify these *in silico* predictions *in vivo*, thus offering verification of the effectiveness of the procedure as well as feedback to develop it further. As emphasised by the Leader of FIMM, this connection to the clinic is what makes their research the "systems medicine" rather than the "systems biology" approach.

This section has offered insight into the systems medicine approach at FIMM as it is connected to their ISM grand challenge. I have focused on explaining the difference between the systems biology and the systems medicine approach. What is still missing from this description is the relation between different kinds of models used to study drug effects, including *in vitro* cell lines and *in vivo* animal models. In what follows, I will examine the ways in which these different models were seen in relation to FIMM's systems medicine research and what kinds of methodological challenges the validation of these different kinds of models brought to the work at FIMM.

2. Methodological Challenges in Systems Medicine Research

In the ISM project, as exemplified with the analysis of the AML pilot project, FIMM's researchers evaluate the data integrations through a comparative analysis of different kinds of models. In the AML example, the *in silico* predictive models essential for the systems medicine approach are developed in relation to the data generated from cell samples that are used to model differences within one cancer type. In this case, the data generated with the DSRT

platform and molecular profiling was based on patient-derived *ex vivo* cancer cells but similar filtering process, when evaluating existing studies on cancer molecular profiles, could also be done with *in vitro*[248] cell lines. As written in FIMM's webpage which explains the ISM program, one of its main goals is the "[i]ntegration of in vivo, ex vivo and in vitro data: Model systems will be designed to understand mechanisms and causalities, such as drug combinations, based on ex vivo data from patient samples. Thus patient samples and models are compared to one another."[249] This section will clarify how these different models are linked together and what kinds of methodological challenges this produces. I will, first, explain the differences between *ex vivo*, *in vitro* and *in vivo* models. Then I will consider how information generated from these different models, including *in silico* models, are validated in comparison to one another. Finally, I will analyse the interdisciplinary requirement this validation process brings to FIMM's research.

2.1. Differences and Connections between *Ex Vivo*, *In Vitro*, and *In Vivo* Models

Both patient-derived cancer cell samples and cell lines are processed *in vitro*, meaning that they are studied outside the living organisms and, thus, cannot fully model how cancer cells function in their *in vivo* living context. Nevertheless, the patient-derived cell samples are referred as *ex vivo* samples because they are seen closer to the actual patient's living situation than the cell lines maintained *in vitro*. Furthermore, cell lines, like individual *ex vivo* samples, always represent a certain kind of molecular profile. However, while multiple *ex vivo* samples then represent different kinds of molecular profiles, similar multiplicity is difficult to replicate with cell lines. As Researcher 8 underlined,

> once you take the cancer cells out their setting in the patient, eventually they start changing and if you make a cell line—not all, far from all, samples can be established

[248] As translated, "in the glass".
[249] < https://www.fimm.fi/en/research/grand-challenge-programmes/individualized-systems-medicine-cancer> [Accessed 21.12.2017].

> into cell lines—you make a sort of selection of certain types of cancer, often subtypes of the cancer that you grow out to consider in terms of genetics (…) the spectrum of mutations, and so on, they have in patients may be quite different compared to cell lines because there's only certain types that actually grow out.
>
> (Researcher 8)

This excerpt helps to explain why FIMM's research uses more *ex vivo* samples than *in vitro* samples in their ISM project. Firstly, it is challenging to create immortal cell lines from cancer patients because most cells derived from patient tissue samples do not continue dividing in the laboratory circumstances but die rapidly. This is why cancer studies for a long time relied on immortalised cancer cell lines that, due to a mutation, will continue to divide indefinitely also outside of the body. One of the best-known examples is the HeLa cell line, which is based on cancer cells that were taken from Henrietta Lacks in 1951. These cells had a naturally occurred mutation, which enabled them to divide even outside of her body. Due to its immortality, the HeLa cell line became one of the most used cell lines in medical studies.[250] While this immortalisation can now be done artificially, Researcher 8's statement above makes it clear that this is still a difficult procedure and not always successful. Thus, *ex vivo* samples offer a more suitable basis to model differences between patient groups within a cancer type. In addition, to predict the drug functions for individual patients it is necessary to perform the DSRT studies with *ex vivo* samples derived from that exact patient.

However, in the basic research *in vitro* cell lines are sometimes needed as well. This is because it is much easier to use them multiple times. As Researcher 8 pointed out, "often the advantage of the cell lines is that you can go back to them unlimited number of times but the patient cells and *ex vivo* cells are a limited resource."[251] Thus, the *in vitro* cell lines can be used

[250] For the history of Henrietta Lacks and the HeLa cell line, see Skloot 2010.

[251] While numerous biobank initiatives are now aiming to freeze and store patient-derived samples, which would allow their continuous use, Researcher 8 noted that it is still the best to analyse *ex vivo* samples as soon as possible as freezing can influence the cells. Difficulties in the standardisation of biobank samples are also discussed in Marcus and Cesario 2011, 10–11. This is why many researchers still prefer using cell lines in their research.

to, for example, verify predictions made by *in silico* models before moving into possible clinical translation approaches with *ex vivo* samples.

The *in vivo* model, quite literally, refers to studying how certain functions occur in the living organisms. In the AML pilot study, the *in vivo* verification referred to the patients who were prescribed drugs based on their *ex vivo* sample analysis. This verification process is essential to the development of the use of drug sensitivity predictions in the clinic as the *in vivo* information helps to assess whether the *in silico* model based on the data generated from the *ex vivo* sample is accurate and, also, to develop the procedure further after patients form resistance to the prescribed drugs.

Still, often in medical research *in vivo* models refer to animal models. At FIMM, Groups F and H that were not actively participating in the ISM program, but were listed under FIMM's systems medicine research, used animal models in their research on lung and breast cancer. The research groups connected to the ISM did not have their own animal models, though some of the researchers also in these groups mentioned that they collaborated with Group F or with researchers outside FIMM to provide animal model based data to their research. However, as Researcher 12 said, in the ISM project *in vivo* animal models were mostly seen outside of FIMM's research scope as their main goal was to use DSRT led studies to provide filtered data that, for example, pharmaceutical companies could then use in their own further studies, including animal models. In other words, the aim in the ISM project has mainly been to generate data and develop integrative models that would reflect patient heterogeneity in drug resistance in the studied cancers and, in that way, help in drug development and clinical trial designs. However, as explained, this goal does include direct treatment prediction models and also research on basic cancer mechanisms to identify cancer subgroups. Thus, the need to model basic cancer mechanisms that could help to explain genomic variations between patients and their drug responses also creates methodological challenges in model production and validation.

2.2. Methodological Challenges in Model Production and Validation

What is often highlighted in the descriptions of systems biology is its a methodologically new way to approach biological organisms. The enormity of this shift is often explained through a comparison between physics and classical molecular biology. Contrary to physics, where mathematical formulas have been more easily fused together with experiments, biological research has been less willing to establish any general laws about the organisms as it is more experimentally based.[252] However, systems biology aims to alter this distinction by examining dynamical functions in the organisms rather than reductive linear causal mechanisms that rely especially on genes as the explanatory units. As Stefan Hohmann, whose research group has developed models for cell signalling pathways, writes, "[s]ystems biology attempts to apply the rules of physics and mathematics to achieve a rational understanding of biological phenomena."[253] In other words, whereas systems biology relies on quantitative research where big data helps to establish possibilities for more general understanding of studied phenomena, classical biological research is more tied to researchers' abilities to construct good models to study the research hypothesis. Thus, the resulting analysis is often descriptive in its form.[254]

However, the aim in systems biology research to establish a link between theory and experiment creates methodological problems as "[r]elating dynamical and mechanistic accounts is a huge challenge. The tools and reasoning of mechanistic researchers and dynamical systems theorists are very different."[255] Still, relating these two approaches is necessary as biological experiments generate data for computational models and help to test and validate these models. In other words, the *in silico* simulations, modelling functional systems-level dynamicity, need

[252] See Keller 2002, 1–3.
[253] Hohmann 2017, 127.
[254] Ibid. For sociological accounts of how classical biological models are build see, for example, Knorr Cetina 1999, chapter 2 and Latour 1999, chapter 4.
[255] Bechtel 2017, 33.

to be developed in relation to biological experiments that have been seen as obstacles in producing such models in the first place.[256]

While FIMM's systems medicine research has a pragmatic focus on drug effects, they also face the challenge of integrating different kinds of data. Moreover, as Carusi has argued, a move from systems biology to systems medicine brings new methodological problems or, at least, highlights the existing ones. This is because the systems medicine approach needs to consider both general disease mechanisms and variation in patient cohorts to develop clinically relevant simulation models. In drug studies, for example, researchers need to take into consider that patients can react to same drugs in different manners or they might need a different dose from one another or different combination of drugs.[257] The challenges that this patient heterogeneity brings to the study of drug-effects was evident in FIMM's aims to form drug combination plans for individual patients.

An important part of FIMM's ISM program is to plan "strategic drug combinations"[258] that can help boost the effect of drug therapies. The hope is that the drug combinations would help to better fight against the cancer forming resistance to the treatment. However, while certain drug types can indicate a cancer subgroup in FIMM's DSRT led studies, the drug combinations often cannot be based on these subgroups but they need to be individualised. As Researcher 8 said in the follow-up interview in 2017,

> [When] we look at the single agent level, we see across the cohort of the disease patient samples—with, supposedly, one disease—we see heterogeneity in responses. But then we do the combinations, then we see another layer of heterogeneity. So it does get complicated, little bit discouraging. (…) There's certainly certain sort of second drugs that tend to boost it more but it's not in all cases, so it's the second layer of heterogeneity that emerges often.
>
> (Researcher 8)

[256] Carusi 2014, 31.
[257] Ibid., 32.
[258] < https://www.fimm.fi/en/research/grand-challenge-programmes/individualized-systems-medicine-cancer> [Accessed 22.12.2017].

This comment highlights the difficulties, even when pragmatic focus is on drug effects, to create predictive models due to patient variation. Furthermore, the right drug combination is not only related to the drugs that are prescribed but also the amount and timing of when the drugs are taken. These considerations need to also be taken into account in the study design. As Researcher 8 explained,

> if we look across the cohort and a certain drug, in some cases we see very strong sensitivity to start with so we don't need to boost that. It's more the ones who receive intermediate response that is something that can be boosted up (…) [and] you can think this in different ways. The simple assay of taking few thousand cells and trying one drug to see how many we kill may not be the most relevant way. Maybe [a better way is] that you take Drug 1 and over time some cells escape that and that's when you need Drug 2. So then you need a different experiment, you need a longer experiment and see that what really happens is [that] when you take Drug 1, eventually the cells start growing back because they develop resistance and they avoid the drug—they may not die from the drug but stop and sit there for a while and then they find a way to work around it or because there's certain mutation that provides resistance—and that's what you need the second drug for. So, that means longer experiment and we've started playing with those too.
>
> (Researcher 8)

In other words, to predict whether different drugs should be administered in different times requires a longer experimental time than the usual 72 hours used in FIMM's DSRT studies. What is more, the time of the experiment sets limits for the use of *ex vivo* samples as,

> the long-term limits how much you can test but also limits [the times] when you deal with primary cells [as] they may not actually survive that long because sometimes they don't. So then the cell lines can be powerful actually. If you think you have good cell line model of the disease, it's often easier to do with cell lines such experiment. So we do come back to cell lines. But we always, as much as possible, try to work with primary material.
>
> (Researcher 8)

This example shows well that generating data and providing validation for *in silico* predictive models in systems medicine is still dependent on good experimental designs that also bring some limitations to the research possibilities, including what kinds of models can be used for the experiment.

These examples, however, are based on haematological cancer studies. As mentioned at the beginning of this chapter, FIMM's ISM program focused first on AML and other cancers of the blood because the samples were easier to obtain. However, an additional problem that

the researchers face when moving into the study of solid tumours is that in order for the drug testing to be as useful for the treatment planning as possible, the cell samples put through drug screening have to mimic the reality in which the cancer cells exist in the human body—as part of cancerous tissue. As the aim in FIMM's ISM program is to develop individualised treatment options also for solid tumour cancers, this difficulty in modelling cell-tissue interaction has led some of FIMM's researcher to investigate ways in which they could make patient-derived cells grow on top of one another *in vitro.*

During my fieldwork, I had the chance to observe a research meeting focused on discussing how this aim was developed with prostate cancer cells. This was not the first meeting I observed, but it was the only one where collaborating doctors, three of them in total, were participating as well. In the meeting, Researchers 13 and 14 from Group A presented their work in modelling prostate cancer samples. They highlighted the difficulties in mimicking tissue environment in prostate cancer. Different parts of the tumour can have different kinds of cancerous tissue, thus raising the concern that a cell sample taken from one part of the tissue might not represent the whole tumour. In addition, researchers were faced with the problem of how to model the fact that cancerous cells do not grow separately in the tissue but in close contact with one another. This means that drugs that might show good response when studying their impact on individual cells, might not have a similar reaction when introduced to the whole body. For this reason, a lot of discussion in the meeting was focused on Researchers 13 and 14's attempts to grow 3D models of cancer cells, meaning that cancer cells could be made to grow on top of one another in a petri dish, thus offering a better model for solid tumours.

This model development had, however, an even more fundamental challenge to overcome before developing multidimensional cancer cell models would be possible. The challenge with the cells derived from patient tissue samples is that they die shortly after removed from the body. As mentioned, this is why cell lines are used in research. While patient-derived cancer

cells can be turned into conditionally reprogrammed cells (CRCs) and used similarly to immortal cell lines, FIMM's researchers also faced another challenge; to develop a procedure in which CRCs also mimic the molecular environment of the parental tissue, meaning the patient tissue sample from which the cells were originally taken. As prostate glands can include five different kinds of cells, it is essential that CRCs' molecular profiles matches that of the parental tissue.

During the meeting, Researchers 13 and 14 introduced a study in which they had aimed to produce such CRCs.[259] They had been able to successfully conditionally reprogram cells from seven different patients, including samples from two patients' benign tissues and control samples from people without prostate cancer. However, during the meeting it became evident that only in one case the CRCs matched the molecular profile of the parental tissue. In other words, only this one case could offer relevant indication of how the tested drug combinations might affect the patient. This led to a situation where most of the meeting was circling around a patient, coded as HUB.5. The patient was seen as "the most central patient" in the meeting, because the CRCs reprogrammed from his cells were the only ones that could give usable drug screening information.

HUB.5 had an aggressive prostate cancer, and he had already received standard androgen-deprivation therapy. This kind of treatment is also known as "castration" as it targets male hormones in the prostate glands in order to stop the production of testosterone that aids the growth of cancer cells.[260] HUB.5's cancer had become resistant to hormone treatment, developing into castration-resistant prostate cancer (CRPC). CRPC state is currently treated with few drugs, some of which are cytotoxic, meaning that they kill normal cells in addition to

[259] The outcome of the study was published in 2017. See Saeed et al. 2017.
[260] History of using hormone treatment in prostate cancer, as well as in breast and ovarian cancers, can be read from Mukherjee 2011, 213–214.

cancer cells.[261] Still, these treatments eventually lead to the relapse of the patient and therefore new drugs are needed to better treat the CRPC state.

After informing the doctors and other participating researchers about the success of creating CRCs from HUB.5's cells, the discussion proceeded to the results of the DSRT test. One drug, called Navitoclax, had showed a good response on HUB.5's CRCs. As Navitoclax was not a commercially available drug but was under a clinical trial with CRPC patients, the discussion moved on to the possibility of sending CRCS patients to Pennsylvania where the clinical trial was held. The possibility to create their own clinical trial in Helsinki was also considered.

Among the versatile discussion of challenges in tissue modelling and DSRT-based treatment options, a short dialogue suddenly vividly reminded me of the importance that cancer subcategories play in FIMM's systems medicine research:

– Did he die of prostate cancer?
– No, he died of something else.

HUB.5, "the most central patient", had already died. The reason why his CRSs were so central for the studies and why the result of the DSRT performed with his CRCs were relevant was because they could give indication on how to treat other CRCS patients even when this information came too late for his own treatment.

The HUB.5 case illustrates both the difficulties in relation to biological experimentation design as well as how these challenges posed for model construction are related to the requirements for systems medicine to account for variation in patients. Moreover, it reminds that subcategories have an essential role in the development of individualised cancer treatment. Therefore, experiments done with different kinds of models can all contribute to systems medicine research, either by generating data for *in silico* studies or validating them.

[261] The logic of using cytotoxic drugs is that they first target the cells that divide rapidly, such as cancer cells. This is why hair loss is a side-effect of chemotherapy as the drugs also kill the fast dividing hair follicles.

Furthermore, HUB.5 case shows that the development of integrative *in silico* models requires not only mastering of computer and mathematical modelling but also the construction of good biological experiments, in this case production of CRSs for 2D and 3D models, that can generate relevant data. This in effect has required interdisciplinary collaboration in FIMM's system medicine research.

2.3.Interdisciplinary Collaboration in Systems Medicine Research

In order to make sense of how a systems approach functions at FIMM, it is necessary to consider not only how a computational approach is needed in systems medicine research but also how research combines researchers from different scientific disciplines. As Miles MacLeod points out, after conducting five years of fieldwork in two systems biology labs with Nancy Nersessian, if one wishes to understand systems biology research, it is important to consider how systems approaches require different scientific disciplines to collaborate.[262] It is important to understand that systems approaches do not only mean application of different levels of modelling but also collaboration between people who are educated to master these different research methods. Hence, if one wants to understand how cancer systems medicine functions in practice, it is essential to consider how the new technological and mathematical approaches have not only shaped our understanding of what constitutes cancer research but also *who* can be a cancer researcher.

The need to combine information from different levels of cancer biology requires collaboration between different researchers, as most researchers are not educated in all areas of research. This has drastically changed daily work for many cancer researchers. As Researcher 13 explained in the interview,

> When I was doing classical molecular biology, I was the one who started and finished the experiment. I controlled every part of it. Now that has changed. It is still me who decides

[262] MacLeod 2015, 95.

> what I want to do but then I take it to [Laboratory Coordinator 1], who's our expert in robotics and drug substances and she helps me to design the experiment and puts the drugs to the places I want them to go. And then it goes to the lab. I don't do that now myself [because of time] but if I would do it myself, I would put the cells on top of the drugs. After that [the cell plate] could go, for example, to our imagining experts who would take pictures of the cells for me. After that it would go to informaticians specialised in imaging, who would then bring the data to the statistics, who then would bring it to me. So that's the whole process for getting the results, which is quite different from classical molecular biology.
>
> (Researcher 13, my translation)

While this quote highlights the changes in data gathering process, it is also important to understand how the analysis of the data requires understanding of how every step of processing the data uses a different methodological approach. Thus, the collaboration in systems medicine is dependent not only on combining different methods of processing the data but understanding how to combine and integrate the information gained from different approaches. Thus, systems approaches are often defined as "interdisciplinary" because of the need for close co-operation between scientists from different fields, such as computer science and cell biology.[263]

Philosophers of science such as MacLeod and Marta Bertolaso indicate the epistemic changes that systems approaches have brought to biological and medical research and which, in many ways, help to explain the experiences that FIMM's scholars have in their daily research trying to collaborate with researchers from different disciplines. As PhD Student 3, working in Group E, mentioned when asked about possible difference to their previous experiences,

> This is quite different [to my previous studying place] where we all just sat and coded silently in our own corners (…) here we have people from very different backgrounds and you have a lot of hands-on work and experiments. We need to communicate and work together a lot more when we are trying to combine, for example, my know-how and someone's expertise in [wet]lab work and because of that we have to work with one another much more [than in my previous place].
>
> (PhD Student 3, my translation)

As highlighted by PhD Student 2, from Group B, the main issue raised when asked about the challenges of collaboration at FIMM was the need to learn to communicate with people from

[263] This is why philosophers of science, such as Macleod and Marta Bertolaso, have emphasised the importance of interdisciplinary collaboration when applying systems approaches to biological research. See Macleod 2015 and Bertolaso 2011.

different disciplines. For example, Researcher 1 replied when asked whether the collaboration is challenging,

> It is challenging. Even in one disease we have collaboration between computational modellers, like me, experimental researchers like with people from [the Groups A and C] and then with the clinicians, who come more from the side of clinical drug development. It takes time to have these groups and people to talk with one another and then to make things together. But now it is going well.
>
> (Researcher 1, my translation)

One reason for communication barriers in research practices comes from the fact that researchers coming from different disciplines do not always fully understand what limitations a certain approach has. For example, PhD Student 1, from Group C, whose project focused on studying drug responses in *in vitro* samples pointed out that it was occasionally challenging to make computer scientists understand that biological experimentation has to always deal with a margin of error as so many things can affect an experiment whereas mathematical modelling is much more precise.

The "mediators" in the groups, meaning researchers who had previously studied both computational science or bioinformatics and cell biology, often facilitated these kinds of daily research challenges. PhD Student 2, from Group B, who described himself as this kind of mediator, stated that other members of his group often asked for his help in how to model biological data. Many researchers with a computer science background also mentioned that they tried to actively learn about cell biology and asked help only when they could not find the answer themselves. These examples show methodological challenges in interdisciplinary collaborations.

Some of the ways to aid interdisciplinary collaboration were less linked to communication and methodological challenges and more to the organisation of the work between people from different disciplines. When I talked with PhD Student 6, who worked as a bioinformaticians in Group A, he noted that it had been sometimes difficult for him to conduct his work in a research

lab where he collaborates with biologists. He stated that this was especially the case at the beginning as,

> At FIMM, my own interest was more on linking gene expression data and drug sensitivity. But then in the beginning the way that FIMM was set up, the unit was already running, different groups were running their own screens so you do a screen and take your data to your project and it would be very hard for informaticians like me to get a hold of the data and look at the big picture.
>
> (PhD Student 6)

Thus, while biological experiments generated data at FIMM, this data was not collected together in a way that would enable informaticians and computer scientists to access it and use it for their own research. Moreover, helping biologists to interpret the data from their experiments could take a lot of time from informaticians and be repetitive in nature. As PhD Student 6 explained,

> as bioinformaticians, we were also faced with a problem of analysing data for different projects so you do the same thing for many people. You come to me that you want this to put in your analysis, after doing it for you, I do it for [Researcher 13], I do it for [Researcher 15], I do it for [PhD Student 7], like all the biologists, and you can imagine how much time I spent doing that. These people could automatically do the same analysis by themselves, because I have done the same analysis, it's like a routine.
>
> (PhD Student 6)

To address both of these problems, PhD Student 6, together with few other PhD students and Researcher 13, had developed a software *Breeze* that would allow cell biologist to insert their data to the program and receive similar analysis as they would gain by collaborating with bioinformaticians. PhD Student 6 described this process,

> We came up with *Breeze* and that has enabled biologists to run analysis by themselves. So the moment the experiment is done in the lab, straight away they put the data on *Breeze*, the data is analysed, it goes to a common database, and they get their results. Meaning that we save a lot of time doing data configuration. Now I have also the data in one place for meta-analysis aiding my tools to become better and understand a big picture.
>
> (PhD Student 6)

The *Breeze* example shows well the challenges bioinformaticians and computer scientists can have in accessing data for their analysis. In this example, *Breeze* helped to organise the data generated at FIMM's DSRT assay tests and made it easier for informaticians to study broader

patterns in this data. However, their wish to open *Breeze* for public use had its own challenges as the collected information, even though coded, was confidential data.

The confidentiality of data also made it difficult for computer scientists to attain non-public data outside of FIMM. While research data is often shared through collaborative projects between researchers, in these kinds of agreements both parties benefit from the exchange of data.[264] Therefore, it can be more difficult for mathematical modellers to gain access to patient data as they do not have data to reciprocate. For example, during my fieldwork in 2014, Postdoctoral Researcher 2 was going through an attempt to study German breast cancer patient samples. He imagined that his hope in gaining access to these samples was based on his abilities to convince the German researchers that his analysis would help to develop the profiling data they have already done, thus, not requiring additional work from their part. These cases show that the newness of systems biology approaches in medical research also means that the practices related to transfers of patient data have not yet come fully in terms of computer scientists as useful collaborators and cancer researchers.

This neglect towards considering such interdisciplinary collaborations caused additional hindrance in regards to academic publishing policies. This influenced especially FIMM's PhD students. As the University of Helsinki is one of the founders and the main host of FIMM, the PhD students at FIMM are students of the University of Helsinki. This also affected the ways in which students viewed the need to collaborate in their projects. The structural challenges posed by collaboration were especially seen in regards to their dissertations for which they must publish 3–5 articles in well-established peer-reviewed journals to graduate. In these articles, students should have their name either at the first or second place in the list of authors. This is because in the medical journals it not only relevant to have your name in the list of authors but it matters where your name is situated in this list as in indicates how much of the work is done

[264] Silvola 2012, 288.

by you. The main author's name comes first and their supervisor's name will appear as the last name of the list, the second researcher comes next and their supervisor's name is the second-last and so forth. This has sometimes caused complications between students due to the collaboration aspect of the projects. As Researcher 8 explains,

> [T]he tradition in the academic research, especially this field, is so much individualised that you need to have your name in a publication and if you're a student or a postdoc you should be the first name whereas the Principal Investigator should be the last name position. When you're someone in the middle, which happens in bigger groups, it doesn't automatically look so good, traditionally. And that leads also to motivation issues for people so we have that with publications here.
>
> (Researcher 8)

Some PhD students pointed out that this had sometimes forced them to negotiate who has the first place in the list of authors as the work had been equally shared. Researcher 13 also noted that, within their group, they had sometimes strategically formed the list so that the person most needing the publication would be placed first. Even with these kinds of group efforts to ease the situation, some students coming from computational science sometimes viewed that their peers, who had cell biology background, did not realise how much work their input had consisted of. It became evident during my fieldwork that many of the PhD students were concerned about fulfilling their dissertation requirements when their project involved close collaboration with other researchers. In regards to article publishing, enforced by the institutional need to publish in well-established journals, collaboration was thus seen as a hindrance.

However, many still highlighted the ways in which collaboration could benefit the value of their publication. For mathematicians and computer scientists, collaboration with cell biologists was essential as medical and biological journals, especially those with high impact factor, were much more likely to publish mathematical results that could be backed up with wet lab experiments. Furthermore, some researchers working with cell lines were collaborating with outside researchers producing genetically modified mouse models in order to provide evidence

that the results gained *in vitro* would be replicable also in the *in vivo* models. Thus, collaboration was mainly viewed as profitable for the aims to publish their research.

Through these examples it is possible to see how institutional settings influenced the ways in which especially PhD students viewed collaboration. While there were some concerns towards rightful merit in publications, I did not encounter any fears that other researchers would steal each other's data or a need to compete with other project members apart when deciding a list of authors for publications. Instead, many researchers at FIMM highlighted that they considered FIMM to be a safe space to discuss their ideas and PhD Student 2 even described FIMM "more like a family".

Attempts to create an open space for communication can be seen as a deliberate aim at the institutional level as the Leader of FIMM highlighted that while there was an intense competition for the PhD places at FIMM, "when they come to our institute, they should not compete but collaborate with one another." This could be seen also in the critical comments of many group leaders towards university's dissertation requirements that did not properly take into account the possibility that PhD students could do their projects in a tight collaboration with the other researchers. Thus, it is important to take into account that FIMM's active attempts to enhance collaboration have to deal with broader structural restrictions that can sometimes make this aim difficult to maintain.

The aim of collaboration in systems medicine is not just to combine knowledge from different disciplines but to meaningfully integrate the know-how gained from data sources, including experimental models, when considering potential ways to develop the computational models, *in vitro* experiments or drug screening processes. However, what is often missing from the philosophical accounts of systems biology approaches in research is the consideration of how institutional settings can influence this collaboration and support innovative research. As became evident during the fieldwork, the daily research practices at FIMM are shaped by the

spatial, personal, structural and societal factors that help also to create collaboration beyond group borders. Importantly, these interactions and innovative research initiatives are actively supported at FIMM. Thus, if one wishes to understand how systems medicine research is made possible at FIMM, and how the ISM program is influencing other research groups as well, it is necessary to consider the operation of the institute as well as its research strategies.

3. Institutionalised Ways in Aiding Innovative and Collaborative Research at FIMM

At the beginning of this chapter, I highlighted variations in responses towards the meaning of the term "systems medicine" from FIMM's researchers. As pointed out, one of the explanations for the discrepancy of researchers' reactions is that only four out of eight research groups in FIMM's systems biomedicine specialisation were actively collaborating in the ISM project, which was usually used as an example of the systems medicine approach. Following Latour's emphasis of the need to address controversies rather than suppress them under the assumed group definition, I came to see systems medicine approach as something which influences research practices beyond the methods used in the ISM program. In addition, not only would it make little sense to leave half of the groups in FIMM's systems biomedicine outside of the analysis but this would also neglect to examine how research innovations and collaborations take place in an institute such as FIMM. In this section, I will examine three aspects that influence FIMM's research: available technology, formal and informal meetings, and obtaining external funding.

3.1. Providing Needed Machinery

One defining feature of systems medicine research is the technological possibility to enhance a mathematical approach to disease research. This differentiates FIMM from a standard

molecular biology research institute, which became evident as soon as FIMM moved into its building at the Meilahti campus. As Coordinator 1, who work as the personal assistant of the leader of FIMM and a coordinator of Group A, and has been working at FIMM since the start, said,

> Before we moved in, we had to change the interior plan by altering laboratory space into office space. They probably didn't consult the researchers or others when planning this space as they didn't take into account that a lot of research is done with computers and we need less wet lab and this kind of space. We have done these alterations pretty much in every wing [of the building].
>
> (Coordinator 1, my translation)

While FIMM still has "wet lab" spaces, which are used for hands-on experiments many of them have been altered into so called "dry labs", that is, computer spaces needed to process the data. While the building was not built for FIMM specifically, it was known during the time of construction that FIMM would be the biggest tenant. Hence, the assumption that molecular biology research would be based mostly on wet lab work was still prevalent when FIMM moved to the building in 2008.

In addition to computer spaces, FIMM's building contains a lot of technological machinery that are essential for systems medicine research. These machines are coordinated by FIMM's technology centre, which also sells its expertise, for example in genotyping and bioinformatics, to national and international research groups, hospitals and companies. One part of the technology centre is the High Throughput Biomedicine Unit, which conducts the DSRT assays. The incorporated technology centre highlights the fact that systems medicine research requires the ability to incorporate technological machinery to collect large-scale data and analyses it with the help of mathematical algorithms. The newest purchase in 2014 was a high-throughput instrument used to study cell-to-cell differences. This is needed as systems biology studies move more towards considering how to account for variation between the cells.[265]

[265] Hohmann 2017, 131.

However, as Researcher 8 emphasised, having the technology does not necessary mean that it will offer better research methodologies. Speaking of the new instrument, he stated,

> just because you potentially have technology doesn't mean that it becomes feasible to [use]. It can be too expensive or so complicated that it's not consistent, but we got great hopes for that. I think that is the main next step. When you buy that there's a lot of development work so we're a bit cautious. (…) There's a lot of people who want to use it when everything is working but not sure how many people there are who want to put the hard-core work on developing all the methods to get that working.
>
> (Researcher 8)

This comments shows that each new piece of machinery is carefully considered in regard to its relevance for the future studies. In addition, it emphasises the extent of the work that needs to be undertaken by someone in creating methods to fit new machinery to FIMM's research. This, again, highlights the fact that biological experiments are never straightforward but each model construction requires extensive and tested study designs to back it up. This is why scholars such as Latour and Knorr Cetina have emphasised the relevance of laboratories and included technologies in providing possibilities to construct a model that can be used to represent the studied phenomena.[266]

One could argue that having the technology centre in the same building is not a defining character, but a tool, for systems medicine research. However, in order to construct good models, scientists need appropriate technologies. There are also practical necessities for having the technology centre under the same roof. As Researcher 8 pointed out,

> [There are] plenty of instruments in Biomedicum [a medical research building next door], especially in imagining so we do co-operate but often it is very inconvenient if you have to go even to a next door building to do things. You have your experiments; you need to carry them to another building so sometime even going to next-door building is too complicated.
>
> (Researcher 8)

While some machinery is shared with the other buildings in the medical campus,[267] it is often important that the research space contains the needed machinery. This enables fast processing

[266] Knorr Cetina 1999; Latour 1987, 1999, and 2005.

[267] One example that I encountered during my fieldwork was the radiator, which was located outside the FIMM building but accessible via the underground passageways. The technician, whom I shadowed while she went to

of information, which also facilitates the interdisciplinary character of systems medicine where biological data needs to be generated from multiple angles as well as return to the clinicians as soon as possible.

3.2. Formal and Informal Meetings at FIMM

At the group and project level, regular meetings supported collaboration at FIMM. The group meetings, that I was allowed to observe, usually consisted of few students presenting the current situation of their own research, which was followed by group discussion. Project meetings, on the other hand, were often more focused on the current situation and possible challenges in the project. In the case of the ISM project, some members felt there could have been more meetings and clearer structure deciding who does what in the project. As Researcher 8 stated in our interview in 2014,

> We have some meetings. Initially every two weeks, but they grew too big. Now [we have them] once a month. Sometimes only group leaders and senior researchers [attend]. It has been a challenge. We don't have a strict plan, who does what (…) We work quite independently, not feeling controlled but sometimes there is the issue of whose responsibility it is to do this. It has happened couple of times between groups that two groups have worked towards the same thing, side by side, rather than working together or choosing that you do this [and I do this]. But one issue, I think, is that there are many things that we never get to, that we feel are, could be burning issue, but nobody….so we could certainly benefit from more strategising of what we… but there's also the difficulty of doing academic science. Independent groups. So nobody really has the mandate of "you should be doing this in terms of from group A to group B"
>
> (Researcher 8)

While people taking part in the project had their own specialisations, often connected to their research group, the above quote shows how demanding it is to organise how the data is generated and integrated. As Researcher 8 continues,

> we have done that now, we have done testing [the procedures]. Challenge is who has to write the data. But the concept we are trying to have is that it is basically everyone's data

radiate the cells in order to make them suitable to become "feeder cells" that would enable cancer cells to grown in a petri dish, mentioned that she had to go to the radiator three times on a busy week and sometime needed to go back-and-forth as the radiator can only contain ten petri dishes.

> and everyone can work on it. Obviously, express what you are doing with the data so that people know and many people don't do the same thing.
>
> (Researcher 8)

These comments show that project-based meetings were not frequent enough to ensure effective collaboration. In this light, it is important to consider how FIMM at the structural level aimed to generate informal meetings.

There were active attempts at FIMM to support informal meetings between the personnel. Speaking with Coordinator 1, it became obvious that the role of communication between researchers, even if they did not share a research project, was seen as essential for the success and effectiveness of research at FIMM. She emphasised the role of the "Thursday coffee sessions", a meeting held in every two weeks where few researchers could present their current project. This meeting is held in the common lunch area. According to her,

> It is also good that people learn to go [to the lunch area] and meet people because most of the people have an intensive working schedule and don't meet people from the other groups. This means that there is too little of this kind of interactivity, which is not related to some meeting or an established research project. Even the [annual] retreat is full of science from the morning till the night. The situation has now improved, but we had to step in a few years ago and organise possibilities for people to meet and discuss what they are doing in their groups, what are their specialisations and, on the other hand, what kind of help and technology they would need. [We had to step in] because people were buying or using outside services that we could have provided within the house. That was the time when the institute suddenly grew bigger, different technologies, groups, people and projects were coming in and it took time before things settled down and people became aware of what other things were going on in the institute
>
> (Coordinator 1, my translation)

This quote highlights how institutes such as FIMM need to actively ensure that the researchers are aware of the other research and technological possibilities at the institute. This becomes especially important in the systems biology approach which, as MacLeod and Bertolaso have emphasised, has to continuously question how to better generate and analyse biological data. While this quote highlights the need to inform the researchers about what is happening in the institute, Coordinator 1 continued by elaborating how this is also an issue of creating a space for informal discussion,

> While things are better now, all the meetings such as the coffee breaks allow people to talk more freely five minutes before or after the presentations. Talk about things that are not related to any agenda but talk about work more freely, which is a very positive thing. When I started working at the Genome Centre ten years ago, which was located right there in the Biomedicum 1, the discussions where you could talk with people outside of your immediate work always took place in the smoking area. But now, when less people smoke, we don't have that anymore. Back then you had ten to fifteen people with various mixtures always standing in the same place at the same times and all the information was travelling exceedingly well. As this has now decreased to a large extent, we need something to replace it. That doesn't happen on its own as everyone is busy and working, founding, building and planning something new. In all of that, you don't have much time to think 'whom should I meet today?' That is why it is important to start it. Now people already know one another and there is collaboration beyond the group borders and I think that groups know now very well what our technology centre can offer.
>
> (Coordinator 1, my translation)

The vivid example of the previous role of the smoking area shows how Coordinator 1 had noticed the need for the researchers to have a space for informal meetings as this will help information to spread within the institute. While she also highlighted the need for more official information channels, such as institutional meetings, in facilitating spreading of information about the research protocols, she still considered these informal meetings as one of the best ways to support research collaboration.

I gained more appreciation towards this active strategy when I discussed with Postdoctoral Researcher 3, from Group A, who had presented her research on the role of extracellular vesicles in the communication between cells in Thursday's coffee break meeting at FIMM. This presentation led her to discuss her methodological challenges with Researcher 10, who was a group leader from the human genomics side of the institute, which directed them towards a joined project as they shared interest on studying extracellular vesicles. Coming from different specialisations of the institute, these two scholars might not have otherwise met and formed collaboration. Thus, the example of organising meetings in the common lunch area so that it would work similarly to smoking area, offers an interesting insight into how research space at FIMM has been organised to support both formal and informal collaboration between researchers. It is worth noting that these kinds of spatial and meeting arrangements are

knowingly used to enhance intellectual exchange which can even result in unexpected collaborations. Still, most of the interviewees, when asked about co-operation, described their collaborations in terms of research projects or spatial proximity to other researchers. Most research collaborations where based on available funding.

3.3. External Funding

The mentioned examples of institutional frames for collaboration have highlighted cases where collaboration has been shaped or modified in regards to the institutional goals or informal meetings. In addition to these, one of the biggest institutional aspects that influences collaboration is external funding. In 2014, 54% of FIMM's funding came from competitive external funding, biggest sources being Academy of Finland (23%), EU (22%) and TEKES (Finnish Funding Agency for Innovation) (20%).[268] This funding consists of multiple projects, all which are based on a certain broader research aim. For example, the Leader of FIMM replied, when asked about the reason behind having certain EU projects at FIMM,

> We have come to have these projects mainly for gaining funding. But their maintenance is straining, as there is a big competition for the EU grants. Now there is on-going personalised health care call that was not restricted in any way. They are going to fund 3% of the applications. The application process has two rounds, first a 5-page application and then a big application. We have now applied with 10 projects. Why these projects now? They passed. Out of these 10 we hope to get one-third through the first round. I would estimate that one or two of them get funding. It is quite random.
>
> (Leader of FIMM, my translation)

Receiving funding from different sources made the continuous funding uncertain and also took a lot of time and effort from all the group leaders having to ensure the funding for their group, which is often easier for a group led by an established researcher rather than a junior researcher.

[268] FIMM's Annual Report 2014, << https://www.fimm.fi/annual_report/2014/key_figures/index.html>> [Accessed 14.6.2016]

This situation is, however, getting better now that FIMM is starting to gain international recognition as a research institute.

As external funding requires designing projects that fit into the scope of the grant, these funding opportunities also helped to form collaborations between researchers from different research groups. One such example is the Predect Project aiming to help the development of better cancer models. This project is founded by EU's Innovative Medicines Initiatives (IMI) and it connects academic institutes, small to medium size enterprises as well as pharmaceutical companies from EU to work to develop "advanced, transferable in vitro models for breast, prostate and lung cancers."[269] Due to this focus, multiple researchers from different systems biomedicine groups worked in this project, including researchers from Group E and F who did not actively participate in the ISM studies at FIMM. That being said, external funding is not only bringing researchers together to collaborate in these distinct projects. In addition, because the grants can be focused, for example, in systems medicine initiatives, external funding also shapes the methodological approaches. This is one of the reasons why the influence of systems medicine research should be seen as going beyond ISM studies at FIMM.

4. Systems Medicine, Clinical Collaboration and Modelling Complexities

During my fieldwork, I had the chance to attend a symposium "Building Bridges: Personalized Health and Genomics in Clinical and Translational Research" that was organised by FIMM. This symposium aimed to introduce benefits of active collaborations between clinicians and molecular medicine researchers. During the closing keynote, Researcher 3 emphasised the importance of clinical collaboration in basic research by stating, "In the field that we are, don't bother with any kind of biomedical research unless you have a very close connection with a

[269] <http://www.predect.eu/about/> [Accessed 23.12.2017]

clinician and patients. Just don't bother. Because you can't succeed." While it was obvious that the aim of Researcher 3's speech was to challenge audience to critically examine their research, his comment raises an important point about the relevance of clinical co-operation for basic research.

At FIMM, patient samples have an important role in the research of most systems biomedicine groups and clinical collaboration in the ISM project is mandatory to establish the possibility to verify DSRT led predictive models in the clinic. However, it would be misleading to consider clinical co-operation merely as a site where information is brought to. Rather, active clinical collaboration can affect the whole approach that basic research has on studying cancer development, including the cancer model development. Thus, it is important to consider the reverse translation as part of basic research rather than only as its result. As Marcus and Cesario point out "[I]nformation coming from clinical successes and failures (reverse translation) is needed to optimize model development."[270]

The fact that clinical collaboration can shape model production also in the research groups not involved in the ISM project became evident during my fieldwork at FIMM as I started to notice that even these groups had started to evaluate their research in relation to the relevance of active clinical collaboration. During my fieldwork, my interview with Researcher 9, leader of Group F, which is focused on creating *in vivo* cancer models with genetically modified mice, made me consider how clinical co-operation can affect model development. When I asked about the research focus of the group she replied,

> With the mouse models we aim to understand genetic predisposition of lung cancer formation in different mouse models [in order] to understand the biology of the tumour initiation. That is so that we can see what biological processes are common in different stem cell and genotype dependent tumours that we form. [Our work is] kind of biological discovery and understanding [of] how does biology in mouse models teach us about the formation of tumours, not necessarily only related to lung cancer but in general to formation of cancers in biological organisms. The field has moved now from

[270] Marcus & Cesario 2011, 5.

> understanding about the genes and the proteins to understanding how the environment, the tissue, is changing during tumour formation.
>
> (Researcher 9)

However, she then went on noting how the group had recently formed a collaboration agreement with a clinic where they could get samples of lung cancer patients directly form the doctor. She explained the relevance of this co-operation,

> I personally, being a biologist and being interested in [how the tissue is changing during tumour formation], [find it] very difficult to know how you can do that well in a human. For example, immunity is becoming very interesting and I've seen some progress in anti-tumour immunity, immunotherapy, that's very recent in this clinical progress. Understanding how tumours form in the mouse models, we can now ask questions of how immunity in animal models also places a role. In a way, we have a parallel strategy where we're updating ourselves with the literature and the clinical side and at the same time apply it to our mouse modelling experience and that will define the parallel limitations to see what we can do with the clinical samples. (…) But in the clinic, for example, it's only very recently in the lung cancer patients that they screen for molecular profiles, meaning that the scientific aspects are changing also in the clinic and what I aim to do with our research is to form this bridge over research interests to the clinical practices and then see where we go so it's open and continuously changing.
>
> (Researcher 9)

As Researcher 9's comment highlights, the clinical co-operation can be more than just a source of samples or a site for developing better treatment options for patients. It can also offer "parallel strategy" that can help to improve, in this case mice, models in conjunction with the knowledge gained from the clinic about the development of the patient and their molecular profiles.

What is important in this comment by Researcher 9 when thinking about systems medicine research at FIMM, is that while methodologically the ISM program was seen to represent systems medicine, the importance in biomedical research to considering dynamic interactions within and between the cells was also shaping research in groups not actively linked to the ISM program. This corresponds with Hohmann's insight about the prevalence of systems biology in biological research,

> Systems biology on the one hand is an approach to biology (employing the rules of physics and chemistry and integrating experimentation and modelling). But even more importantly, systems biology is a way of thinking about biological phenomena and

> mechanisms: that interaction between biological units (molecules, cells, tissues, organisms) are key to understand evolution and mechanisms in biology. This way of thinking has penetrated biology and medicine to a much more significant extent than the term systems biology as such.[271]

Understood this way, the general impact that systems biology has had on biological research is not only connected to distinct methodological tools but to the new approach to the limits of methodologies seen in biological research. As the methodological limits are pushed forward, systems biology challenges the assumed restrictions inherent in biological experiments and, thus, requires new ways to connect known biological complexity also to biological modelling. In medical research, this means an active collaboration with clinicians to challenge the strict divisions between basic and applied biomedical research as cancer models can be developed strategically in relation to clinical samples and feedback. This collaboration then develops treatment options as has been done in the ISM project.

As was noted already in 2005 when national reports evaluated the benefits of founding FIMM, clinical collaboration and data gathering have been viewed central for the success of the institute.[272] This also has an impact on the ways in which models are developed and paralleled. The cancer research at FIMM is tied to the existence of different kinds of models, including *in vitro*, *in vivo*, *ex vivo* and *in silico* models. These models co-exist not only for clear ethical reasons that restrict the experiments with patients but different models are also chosen based on what kind of hypotheses need to be validated. As Researcher 9's interview suggests, this validation is now more and more defined in relation to the clinical connection not only in terms of possible treatment plans but clinical relevance is used to measure the relevance of the used models and their development is linked to active clinical collaboration. While models in systems medicine do not function as a one-way street, meaning that research would only move towards more complicated models, what is important to realise is that this model comparison is

[271] Hohmann 2017, 130.
[272] Halme 2005, 48.

now increasingly validated in regards to clinical collaboration as has been suggested by Carusi.[273]

Thus, when thinking of practices linked to systems medicine at FIMM it is important to consider them as dynamic. Latour argues that any kinds of hesitance from the actors of the study is important to account in a sociological analysis aiming to comprehend social interactions and phenomena.[274] This is because these hesitations help to illustrate how social formations are momentary associations that do not stand still. Hence, seeming controversies I presented at the beginning of this chapter in relation to FIMM's researchers' definition of their work as systems medicine help to emphasise how systems approaches in medical research are still developing. What is clear, however, is that a systems approach requires new kinds of research collaborations to face the modelling challenges. These collaborations form new requirements for the interactions between basic research and medical care. As the Leader of FIMM highlighted, when discussing the aims of the ISM project,

> To start a new field, and then see where it goes. It is not only about us, about what we do. We have now started a movement, that is followed and everyone is going to the same direction. I think this is a most efficient way to get things done in science, that someone does it first and shows that it works and then people start to get interested and then the others come as well. So in the future, it's not only our input. But naturally we have an interest to continue this activity and the idea is that doctors and treatment go to the same direction. Research activity would influence as much as possible the description of drugs and the individualised care of cancer patients.
>
> (Leader of FIMM, my translation)

What is clear in this statement, is that systems medicine is seen as an approach that requires creating new kinds of relationships between clinics and research institutes. This is why system medicine research influences research beyond distinct research projects implementing big data approach: it challenges the idea that basic molecular medicine research can be performed separately from its clinical applications.

[273] Carusi 2014.
[274] Latour 2005, 46–50.

This chapter has aimed to show what systems biomedicine means in practice at FIMM and how it has influenced modelling methodologies. I have shown that rather than being an established methodological approach, systems medicine challenges the limits associated with molecular medicine research by including big data approaches. In research, this means a need to establish active collaboration with clinicians in order to create an effective framework within which different kinds of models used in medical research can be validated. While model validation could be done, for example, between *in silico* computer simulations and *in vitro* cell lines, patient-derived *ex vivo* samples are needed to establish a basis to study variation between patients. Moreover, *in vivo* verification of the computer simulation models can be done with patients themselves because of the pragmatic focus in FIMM's systems biomedicine research on drug screening. This has also created a new kind of basis to implement basic research into clinical care. I will discuss this aspect in more detail in the next chapter.

Chapter 4

Balancing the Personal and Social

Differences between Personalised Medicine and Gender Medicine

During my fieldwork at FIMM, I attended a lecture by Leroy Hood. Hood had been invited to speak as part of *Distinguished Lecture Series* organised by HUS (the Hospital District of Helsinki and Uusimaa), University of Helsinki's Faculty of Medicine and FIMM. At FIMM, this event had been the topic of many informal discussions I had with researchers well before, all which highlighted Hood's reputation within the field. Hood is known for his work on developing instruments for DNA sequencing and synthesising. He is also known as a leader and co-founder of the Institute of Systems Biology in Seattle. Recently, Hood's name has been strongly connected with systems medicine or, as often labelled, P4 medicine. The four Ps stand for *predictive, preventive, personalised, and participatory*.[275]

During the lecture, Hood described how the long-term aim of P4 medicine is to transform healthcare planning to focus more on optimising wellness rather than reducing sickness with the help of preventive health coaching. He explained this approach with a description of their nine-month pilot study, *The Hundred Person Wellness Project* (100P),[276] containing 108 healthy individuals.[277] The aim of this study was to analyse the progress of the health of these individuals after they had received personalised health coaching. The participants had to take part in regular examinations, including blood samples, and then received coaching based on

[275] See Hood 2013.

[276] The abbreviation HPWP is also used in this project. See Hood et al. 2015. I use the abbreviation P100, which was used in the report of this study (where the study was referred to as the 'Pioneer 100 Wellness Project'), published in *Nature Biotechnology* in 2017. See Price et al. 2017.

[277] One of the participants, however, had to end the project after four months because she became pregnant. During the lecture, Hood criticised the decision but said that, as the cohort was so small, other organisers of the study wanted to preserve its analytical integrity. It is left to be seen whether similar changes take place among the participants of the forthcoming similar study, consisting of 100,000 people, and what kind of impact this could have on the study.

their molecular profile information. The future plan, Hood explained, is to use a similar approach with a bigger cohort of 100,000 individuals to show how the P4 medicine paradigm works in action and demonstrate its usefulness. This, he argued, would also help to study possible indicators of the points in which health turns to disease, which could then benefit preventive healthcare planning.

The relevance of Hood's lecture, and the P4 medicine approach more generally, to FIMM's research strategy became apparent after the lecture when the leader of FIMM who had invited Hood to Helsinki noted that FIMM was taking part in the execution of a similar pilot study, *Digital Health Revolution*, organised by University of Oulu. As noted on the project's website, this study examines "whether returning [personal health] data along with individual lifestyle coaching can contribute to the health of the participants and improve their motivation to lifestyle changes."[278] As noted by Hood, the aim of these kinds of pilot studies is not to treat sickness but to help individuals to maintain and optimise their health, thus transforming what is seen as the main function of healthcare.

The grand idea of altering the healthcare strategy to optimising health seemed, however, rather distant to many of FIMM's researchers. When I talked with them during the coffee break following the lecture, they raised concerns about the practical possibilities to enable such an approach on a larger scale. Also, they questioned what was meant by 'health', how it could be monitored and what was the role of genomics in this definition: could this kind of coaching truly add to our understanding of wellness and healthy lifestyle above the importance of good nutrition and exercise? These reactions raised many questions for me as Hood is one of the main spokespersons for systems medicine and FIMM's research is also dedicated to furthering this field of study. How come Hood's ideas, then, raised so many questions amongst researchers linked to systems medicine research projects at FIMM?

[278] <http://www.digitalhealthrevolution.fi> [Accessed January 25, 2017]

Further examining the doubts raised by FIMM's researchers helps to expand the question presented in prior chapters: to what extent can FIMM's daily research be connected to the aims envisioned in systems medicine initiatives? In Chapter 2, I highlighted that this is a central question when considering the possible role that gendered analysis could have in systems medicine. While FIMM's researchers' work focused on analysing basic disease mechanisms, they saw that gendered differences could play a role when applying molecular-level information to clinical care. The possible future relevance for gendered analysis in systems medicine was further emphasised in Chapter 3, where I showed how one of the guiding lights in FIMM's studies is to bridge the gap between basic research and clinical treatment.

To hear strong questioning remarks towards Hood's lecture from researchers supposedly at the heart of these new initiatives suggests that a more in-depth analysis of the relationship between current systems medicine research and future goals connected with P4 medicine is needed. I wish to show in this chapter that understanding this link between P4 medicine initiatives and FIMM's research is also central when questioning the role of categories such as gender in systems medicine research. The consideration of the relationship between FIMM's daily research and broader aims connected with systems medicine helps to further clarify the differences between the gender medicine and systems medicine approaches and how current research could benefit from gendered analysis.

I have three main areas of examination in this chapter. Firstly, I will consider how FIMM's research is currently applied to clinical practices. I will show that while there's an active collaboration between clinics and FIMM, especially in its individualised systems medicine (ISM) project, direct influence from FIMM's drug-screening results on treatment is still rare. Rather, the translational aspect, bringing basic research to clinical practices, is seen to happen more by aiding drug development towards precision drugs, in collaboration with pharmaceutical companies. However, the research that supports this drug development is

simultaneously seen as a stepping stone towards more individualised healthcare, by producing further information on disease biomarkers linked to certain subtypes of diseases. In other words, supporting what is called 'stratified medicine'. In the second part of this chapter, I will show how this subcategorisation is considered as the basis for forming personalised medicine of the future with the help of the big data approach. I will outline the bigger changes envisioned in this move towards big data medicine that highlights probabilities based on correlation rather than causation in medical decision making. Finally, I will investigate what separates gender medicine initiatives from those of personalised medicine. I will argue, against the claims in the gender medicine literature, that the biggest difference between the two is not whether they include sociocultural information to the research, but where they see the possibilities for preventive medical care. While the systems medicine initiatives emphasise individuals' role in disease prevention, gender medicine also brings forth societal responsibilities.

1. FIMM's Research and Clinical Care

As noted previously, one of the main technological investments at FIMM's systems medicine research is the DSRT platform. This platform is the basis for studying patient-derived cancer cells as their reaction to different kinds of drugs and drug combinations is analysed to reveal the progress of the disease and differences between patients sharing the same diagnosis. This technology also helps to connect FIMM's research to clinical practices, which is significant, as it gives the researchers a possibility to study drug responses in fresh patient samples.[279] In DSRT, if the patient sample contains enough cancer cells,[280] the sample is mixed together with

[279] Obtaining fresh cancer cells, as Researcher 8 explained, was important because freezing the cells can cause stress to them.

[280] Usually, a sample contains hundreds of millions of cells. The DSRT process requires at least seven million cancer cells in the sample. The cancer type affects the density of cancer cells in the sample. For example, there is a striking difference in the amounts of cancer cell density when comparing two haematological cancers: acute myeloid leukaemia (AML) and myeloma. AML samples usually contain more cancer cells. This is because in

different drugs in different concentrations, and sometimes also combinations of different drugs, to see how different drugs affect the sample and cancer cells. The data gained from sample's DNA and RNA sequencing, proteomics and DSRT test are then brought back to clinicians and this information, in some cases, can influence their treatment plans.

The DSRT platform is also at the heart of one of FIMM's main initiatives, the ISM program, which aims to form new ways of facilitating the application of basic research to clinical use. As noted by Researcher 8, the leader of Group C, who has had a big role in setting up the DSRT platform,

> It was set up when we started these types programs together with the haematologists here at the hospital in Helsinki, when they'd send patient samples, cancer cells from patients with acute myeloid leukaemia, and we wanted to test how those cells reply to a set of cancer drugs.
>
> (Researcher 8)

The initiative, coming from clinicians, shows the importance of finding new treatment options for acute myeloid leukaemia (AML), as its chemotherapy treatment options have remained largely the same for over 30 years. This was one of the reasons why AML was chosen as the focus disease on FIMM's ISM pilot project.[281] Also, for FIMM's own research, the importance of bringing DSRT results back to the clinic is noted in one of the firsts publications of FIMM's AML study,

> [W]e present an individual-centric, functional systems medicine strategy to systematically identify drugs to which individual patients with AML are sensitive and resistant, implement such strategies in the clinic, and learn from the integrated genomic, molecular, and functional analysis of drug sensitivity and resistance in paired samples.[282]

myeloma cancer cells are mutated plasma cells, which are very differentiated cells whereas AML cancer cells are developed at the early stage of cell differentiation. This is also why AML is a very aggressive disease, whereas myeloma develops more slowly. The fact that AML samples contain a lot of cancer cells is also one of the reasons why it was chosen for FIMM's ISM pilot study. As FIMM's ISM page states: "Millions of cells can be readily obtained for both molecular and ex vivo drug response studies. Sampling at the time of diagnosis, remission and relapse and drug resistance is easily accomplished." See <https://www.fimm.fi/en/research/grand-challenge-programmes/individualized-systems-medicine-cancer> [Accessed 30.1.2017]

[281] <https://www.fimm.fi/en/research/grand-challenge-programmes/individualized-systems-medicine-cancer> [Accessed 21.11.2017]

[282] Pemovska et al. 2013, 1426.

This excerpt shows how important it is for FIMM's basic research to have an active collaboration with clinicians. The clinical co-operation helps them to access fresh patient samples and, thus, study drug effects in ongoing individual cases. It also allows them to follow-up individual cancer progress. Moreover, this definition of the scope of the ISM program suggests that basic research can be implemented as a part of clinical decision making in real-time—an idea intrinsic to personalised medicine.

However, when I visited Group D, which functioned at the heart of the ISM project mediating between the clinic and FIMM, I gained a better understanding of the limitations of such translation. During my visit, I interviewed three researchers of the group, all of whom also worked as clinicians specialising in haematological diseases. One of them, Clinician 2,[283] had been part of the AML study from the start. After the DSRT platform had been tested with AML samples, the group had started working with other haematological cancers as well, such as myeloma. Owing to the new focus on myeloma, two other clinicians, clinicians 1 and 3, were visiting the group from a university hospital from another city. All of them urged cautiousness when discussing the extent in which DSRT results, together with other personal molecular-level information, can be implemented in medical decision making. Instead, they highlighted that DSRT was unlikely to offer any drastic changes to cancer treatment on its own. Nevertheless, they saw the need to conduct DSRT tests to better understand cancer mechanisms. This, they said, could influence the subcategorisation of the types of cancer that could lead to better screening and treatment of future patients.

While DSRT was originally developed for aiding current treatment decisions, its usage showed benefits for basic research as well. The clinical benefits were, then, further connected to the future treatment options. As Researcher 8 explained the progress of DSRT platform,

> There was the first question (…) would we make discoveries that they could treat the patients with but then, as we started doing it, we realised that we can also, by doing this

[283] While all of them worked also as visiting researchers or PhDs in the group, I will refer to them as "clinicians" to highlight the insights they gave about the clinical relevance of systems medicine research.

> and by looking at the responses of different drugs and patterns of different responses to different types of drugs, then we can learn more about the disease so to go back to the basic understanding of the disease and the individual case.
>
> (Researcher 8)

In what follows, I will offer a more detailed explanation of why DRST results were difficult to translate into clinical treatments decisions. I will, then, move to examine two different ways in which DSRT results were seen to benefit future treatment possibilities through better clinical trial planning and the identification of cancer subgroups. This examination will help to explain how current systems medicine research is connected to the broader aims linked with personalised medicine initiatives.

1.1. Difficulties of Bringing DSRT Results to Patient Care

Most of the patients taking part in FIMM's ISM studies are either relapsed patients or they do not respond to conventional treatment options.[284] This influences the possibilities to apply DSRT results to treatment. When I asked Clinician 3 whether they could apply DSRT results in the patient treatment, she replied,

> Not that much yet. That is because in most cases the samples have been taken when the disease has recurred and it has been treated long already. We have the clinical problem of how to treat these patients. Many of them [have cancer that is] very resistant. They have gone through the conventional drugs and, thus, [DSRT shows] those new molecules that you cannot yet use.
>
> (Clinician 3, my translation)

To find new possible treatment options, and to gain further insight into differences between patients, DSRT includes drugs that are not used for the studied cancer type or have not yet gone through clinical trials and, hence, are not clinically available.[285]

[284] The studies can include samples also from newly diagnosed patients but, as Clinician 1 highlighted, in those cases the DSRT results do not affect the treatment plan but the patients are treated with conventional treatment options. In other words, experimental DSRT-based results are not used when there are still standard treatment options available.

[285] According to Researcher 8, the drugs used in DSRT are selected in collaboration with clinicians and are, for practical reasons, focused more on oncology drugs or, based on broader literature, interesting new emerging drugs.

This causes problems when planning patient treatment as, even if DSRT shows their potential usefulness for the patient, the drugs can be only assigned as off-label drugs (meaning a drug that is approved but used for other diseases), having a patient as a part of a clinical study of the drug, or as a compassionate user (meaning that a patient would be allowed to have unauthorised drugs outside of a clinical trial). In the pilot study on AML, as Clinician 2 noted, this created the problem of finding and obtaining suitable drugs for the patients,

> AML study is based on patients that have no conventional treatment options. Secondly, we needed to find those kinds of leukaemia specific drugs from the DSRT that we could possibly use in treating the patient. Thirdly, what has been a big issue is whether we can actually have access to those drugs. For example, we have had many patients with MEK inhibitor response but we haven't had any MEK-inhibitors available. Only this year, after extensive paperwork, we have gotten those. Summa summarum, those were the reasons why these patients were chosen and who we treated with DSRT-based treatments.
>
> (Clinician 2, my translation)

As he explained, the ISM program struggled to obtain the drugs suggested by DSRT for clinical use.

However, the difficulty in treating patients with DSRT results is not only because the drugs used in DSRT are not yet available but also because of the difficulties in predicting how the drug will function when given to the patient. As Clinician 1 noted,

> If we think of drug studies, we have huge amounts of molecules in the preclinical studies. Some of them end up in clinical studies and many of them are stopped at the early stage, for example, due to toxicity. So, we are very careful. We don't know about the drug's toxicity. Furthermore, the power of the drug, which can seem very good in the petri dishes or rat experiments or other tests, they [then] lack efficiency in the larger human-based studies. (…) We absolutely must note the difference: that this is preclinical research. If it raises some ideas, then good, but it must not ever be mixed with studied phase III research data.[286]
>
> (Clinician 1, my translation)

It is important to note that the treatments given to patients in the ISM study have been either on the process of a clinical trial, which has surpassed the preclinical stage of only *in vitro* or animal-based *in vivo* experiments, or have been commercially available drugs that have been

[286] Phase III clinical data refers to studies that have been tested on a specific disease with 1000–5000 patients. All in all, clinical trials have four stages, the last one being a study of drugs' long-term effects after it has been brought to market.

used for other diseases. FIMM has put a lot of effort in gaining drugs now at the stage of clinical trials, either by trying to get patients to be part of the ongoing clinical studies or by listing them as compassionate users.

Another way to gain access to new treatment in FIMM's ISM program has been to prescribe drugs that have gone through clinical trials but are not currently used for the studied cancer type. Still, Clinician 1 raised issues in using drugs that have been accepted for other diseases,

> It might be that for some [patients] some drug is offered [by DSRT] which is used in some completely other disease, let's say a drug used with rheumatism. We don't know if it has any effect on myeloma or what kind of concentration of it should be given. In case of cancer, we might have to use a bigger dose than when giving it in a disease it has been used for. But we don't know that as we cannot start giving big doses if we don't know the drug. The main principle that we aim to follow is that we cannot harm the patient.
>
> (Clinician 1, my translation)

Owing to these concerns, as Researcher 8 noted, many of the tested drugs in the DSRT platform were used in other kinds of cancers, which would make it easier to support the basis for off-label use. Still, Clinician 1's concerns show well the difficulties envisioned when applying DSRT results to clinical care.

DSRT results, connected with broader information based on DNA and RNA sequencing and proteomics, are, then, not straightforwardly applicable to patient treatment but are always discussed together with the treating clinician. In the end, it is up to clinicians to decide whether these results can be applied to patient treatment. Despite the difficulties in accessing drugs, some patients in the pilot ISM study on AML did receive treatment based on DSRT results. As Clinician 2 noted, when asked how many patients they had treated with the help of DSRT studies,

> We have treated 12–14 AML patients and, out of this group, two have gotten a CR-level response, meaning Complete Remission. Some blood values have not recovered; usually, the thrombocytes did not recover, or at least with these two patients. But these are, of course, very good responses in this kind of patient cohort which is very difficult to treat. But, of course, there is still a lot to improve as well.
>
> (Clinician 2, my translation)

This response shows that despite the difficulties connected with accessing the drugs, DSRT results were still seen as clinically relevant. However, owing to the difficulties of gaining access to studied drugs and the difficulties of predicting how the drug would work in a human body, the main emphasis on DSRT trials has shifted towards establishing a research foundation to benefit future treatment. Clinician 1, who had just joined FIMM as a part of the new myeloma-study, noted that the practical use of DSRT was "more for the future and for research than a treatment base for individual patients." He continued,

> Of course, we hope that it could help with some individuals. That we could find [drug] targets that we could focus targeted treatments to with existing or available drugs. But that possibility is quite small. So, we don't promise anything to the patient. When we're taking the samples [we tell them] that 'it is not likely that this will affect your treatment, but more the future of the treatment of this particular cancer'.
>
> (Clinician 1, my translation)

The clinical relevance of DSRT, and FIMM's ISM program more broadly, hence, is not only connected to its immediate use in patient treatment but its clinical relevance is more based on aiding the development of new drugs and usage of existing drugs. To achieve this aim, FIMM's ISM program relies heavily on pharmaceutical collaboration.

1.2. Drug Development with Pharmaceutical Companies

To support the clinical relevance of their work, FIMM's researchers have also formed collaborations with pharmaceutical companies. The aim is to bring suitable drugs faster to clinical use. As the leader of FIMM stated, when commenting on the aims of FIMM's ISM program,

> [The idea is that] research would affect the process of choosing the drugs as much as possible and support the individualised treatment of the cancer patient. The other thing we try to have influence on is the development of drugs. So that the companies that develop drugs could bring them faster and cheaper to the market and better to the right patients. At the end of the day, this is what restricts our work the most. That we know of good drugs that could work well with the patient but we cannot give those to them as the drug has not gone through the safety testing process. This means we have to do things

> together with the industry, and they are the ones that own our molecules and they are developing projects dealing with this. These are the two lines; to influence patient care and the developing process of drugs. So that drugs would be developed better and faster to the market.
>
> (Leader of FIMM, my translation)

One way to boost drug development is by supporting more efficient clinical trials. This is listed as the final aim in ISM program's list of nine goals: "Aiming to design clinical trials: based on validated results across patients and model systems, building on mechanistic understanding and biomarkers for patient selection."[287] Patient selection here refers to a possibility to focus clinical trials on patients whose molecular profile suggests that they could benefit from the treatment. Clinician 1 described the benefit of this as follows,

> [In order for a] drug to come into the market, you need to be able to show with, let's say, hundred or thousand patients, that most of them benefit from the drug. But if you have a cancer drug that would work with, for example, two patients in a hundred in a large study, then it looks like it has no effect at all, or it is forgotten and the drug company is not interested in it. So it's completely forgotten. In a way, the aim of all this is that we'd find those two patients, with whom the drug works even if it wouldn't with others. This is, I think, what personalised medicine strives to do.
>
> (Clinician 1, my translation)

The fear that drug companies would cease developing a drug that would work only with a small group of patients has a solid foundation in the history of targeted drugs.

One of the best-known examples of a successful drug, which targets a specific molecular profile, is Gleevec. Gleevec, also known as Imanitib, is a drug that inhibits the work of a BCR-ABL kinase. Kinases are central for cell operation as they "act as molecular master-switches in cells—turning 'on' some pathways and turning 'off' others—thus providing the cell a coordinated set of internal signals to grow, shrink, move, stop, or die."[288] BCR-ABL kinase is an outcome of a "Philadelphia chromosome", an aberration of chromosome division in bone marrow stem cells, leading to splicing and mixed reattaching of two chromosomes, 9 and 22. As a result of this reattaching, the genetic material of chromosome 22 is mixed, forming a

[287] <https://www.fimm.fi/en/research/grand-challenge-programmes/individualized-systems-medicine-cancer> [Accessed 30.1.2017]
[288] Mukherjee 2011, 432.

combination of ABL1 and BRC genes. This gene-hybrid then codes a hybrid protein whose function is linked to BCR-ABL kinase, causing the cell to divide uncontrollably. This activated kinase "is present in virtually all cases of chronic myeloid leukemia (CML) throughout the course of the disease, and in 20 percent of the cases of acute lymphoblastic leukemia (ALL)" as reported by Brian Druker and his team in 2001.[289] What made Druker's publication relevant for the development of targeted drug therapies was that it supported the results of previous studies done by his team: that a specific molecule, a BCR-ABL inhibitor, often referred as Gleevec, seemed to offer a good response especially in CML patients.[290] As Siddhartha Mukherjee, a cancer clinician who has traced the history of cancer research in his book *The Emperor of All Maladies* (2011), notes, "Druker's drug left a deep impression on the field of oncology"[291] as most CML patients, whose earlier prognosis had been few years, can now live decades with the Gleevec medication. The success story of Gleevec as a targeted therapy for Philadelphia-chromosome-linked diseases was also noted by Clinician 2 who described it as one of "the few mutations we can currently target in treatment."

While the Gleevec-example shows the potential benefits of molecular profiling in drug development, it also brings forth a question of the economic sense of producing precision drugs as the predicted group of clients purchasing the drug is small.[292] As Mukherjee's work suggests, it was mostly because of the individual efforts of Druker and his collaborators Charles Sawyers, Moshe Talpaz, and John Goldman that the drug ever went through the clinical trials.[293] Mukherjee states that the drug company Novartis, from which Druker had obtained the drug to test with at the first place, was not eager to go through the clinical trials as "CML affects a few

[289] Druker et al. 2001, 1038
[290] Ibid., 1041.
[291] Mukherjee 2011, 439
[292] The expense of developing drugs had been also used as a reason of why new precision drugs are so expensive. In Finland, this has led to questions of what kinds of drugs can be covered by the national health insurance as these drugs are not only expensive but their long-term benefits are still under study.
[293] Mukherjee 2011, 436.

thousand patients every year in America. The prospect of spending millions on a molecule to benefit thousands gave Novartis cold feet."[294]

The story of Gleevec illuminates why FIMM's ISM strategy emphasises the need to better design clinical trials. As more and more demands have been made for creating individualised treatment options, also pharmaceutical companies are pushed to develop more precision drugs.[295] In this light, it is noteworthy to return to FIMM's leader's comment about the need to not only support better and faster drug development but also cheaper. The idea, then, is that FIMM's research could help to reduce the cost of drug development, making the future precision drugs possibly less costly. What this idea brings forth is collaboration between research institutes such as FIMM, which focus on understanding basic disease mechanisms to help to identify subgroups in cancer types, and pharmaceutical companies that can develop drugs to benefit this subgroup. FIMM's research's clinical relevance is, thus, not only tied to direct clinical treatment applications but also to aiding industry in drug development.

To gain a better understanding of FIMM's collaboration with pharmaceutical companies, I returned to FIMM in 2017 to interview Researcher 8, whose role as a principal investigator of Group C positioned him as one of the contact people between pharmaceutical companies and FIMM. He emphasised that it is important to see this collaboration as mutually beneficial. He noted that the first collaborations within the ISM project, which are also still common, were ones where pharmaceutical companies wanted to test their drugs in the different platforms that FIMM has. While these agreements bring funding to FIMM, Researcher 8 noted that the basis of this kind of agreement should be whether results would be of possible interest to FIMM's research aims,

> The question is: is that interesting to us or is that just contract research, as contract research is not the most interesting thing we can do you know (…) [We] should be a research-based university institute. So then the question is, is that of interest for us, is

[294] Ibid.
[295] Olivier et al. 2008.

> there something that we can get benefit from. So we need to work out the contract so that we actually learn something from it too.
>
> (Researcher 8)

By differentiating FIMM's collaboration from contract research, Researcher 8 makes it clear that FIMM's role should not be seen as one only supporting the pharmaceutical industry. Rather, FIMM should be regarded as a research institute that can develop its own agenda through collaboration with the industry. The reason why it is important to emphasise whether studied drugs are of interest to FIMM's own research aims is because, in these kinds of company agreements, collaboration does not extend to the actual studies. Instead, FIMM receives funding to set up the drug trial and reports the results that can then be followed up with new tests. To ensure that the study is non-biased, there can be no influence from the company providing the tested drugs.

When FIMM's research started to gain an international reputation, it also became easier to form collaborative projects with pharmaceutical companies. One such example was collaboration with Pfizer in a study of testing the possible benefits of a renal cancer drug to chronic myeloma leukaemia (CML) patients. This collaboration, as Researcher 8 narrates, started from FIMM's own research on CML,

> It started as an independent finding - we had then bought that compound from a commercial vendor and tested it with these patient samples with chronic myeloid leukaemia that had become drug resistant to the standard drugs and saw that this drug induced a strong response in these cells. And then we went and talked to Pfizer and then we happened to stumble on the right people - there was also a stroke of luck in that sense because Pfizer is a huge organisation.
>
> (Researcher 8)

One thing that made this kind of collaboration possible and supported FIMM's role as a research institute in pharmaceutical collaborations is that the drugs that FIMM uses in the DSRT platform are commercially bought; their amount went from over 300 in 2014 to over 500 in 2017. This way, FIMM's researchers are not restricted in how they can use them. As Researcher 8 noted, "the pharma collaborations and company collaborations involve more proprietary

things that we only use specifically for those projects and we can't use otherwise. (…) So, there we avoided to have things restricted and come from pharmaceutical companies." This way, as was the case in the Pfizer collaboration, FIMM can perform their own studies and approach pharmaceutical companies when they already have insight into the drug's potential usefulness.

After gaining interest from Pfizer, the following co-operation was much more active than in previously mentioned cases of drug testing. This meant that FIMM's researchers could also gain from research co-operation with Pfizer,

> [T]hen we really started working on both ends towards this—the Pfizer team was able to do things that we couldn't do. The structural biology and this and this [of which] we don't have the expertise—we could have probably found people but it would have taken a long time—they're very good at it so they did it very quickly and very well. And they had other pieces of information that we didn't have so when we merged together we were able to get a very nice story.
>
> (Researcher 8)

This example shows how pharmaceutical collaboration could bring, in addition to funding, know-how for FIMM's researchers. This additional source of information is valuable for researchers, as the emphasis of FIMM's research is not only on locating suitable drugs for current patients but identifying patterns from very heterogeneous patient data.

On the other hand, collaboration with FIMM is useful for pharmaceutical companies as they can gain access to the information based on fresh and frozen patient samples. As Researcher 8 noted, one of the biggest assets that FIMM has in attracting company collaborations on haematological cancer studies is their connection to the haematology registry and clinical biobank, stored in FIMM's facilities, that has been the basis for the ISM program at FIMM. The biobank also enables FIMM's broader research aim, which is also an aim where FIMM's and pharmaceutical companies' research interests coincide: detecting disease patterns from heterogeneous patient cohorts.

The aim of systems medicine research at FIMM is not only to treat individual patients but to learn about cancer mechanisms at the same time. The latter requires a comparison between

cancer cases. What is more, to say something general about cancer, such as forming a new cancer subgroup, requires a large number of patient samples. Therefore, biobanks are seen as central for systems medicine research. As noted by Researcher 8, especially in the case of rare diseases such as AML, it is essential to be able to store frozen patient samples, which allows researchers to return to them. As Researcher 8 notes, "as we learn more things we might start thinking that this certain type of leukaemia may be related to another subset of that because of mutations and then we can test that." As cancer samples are very heterogeneous, biobanks also allow the forming of larger sample collections that support efforts to enable big data approaches in medical research. Bigger sample collection, together with the DSRT platform, helps FIMM's researchers to locate biomarkers that can be used to identify cancer subgroups. This broader aim of FIMM's research also links it to the future aims of personalised medicine initiatives.

1.3. Biomarker Identification in the Subcategorisation of Diseases

The fact that patients with the same cancer diagnosis react to drugs differently emphasises the need to identify cancer subgroups. This, however, requires attention to basic cancer disease mechanisms in an attempt to understand disease pathways. As noted in Chapter 3, FIMM's systems medicine research is focused on a practical quest to identify disease biomarkers, in other words measurable indicators from biological samples identifying a certain pathological or physiological process, that could be used in healthcare to predict disease, diagnose it and treat individuals. By identifying disease biomarkers, FIMM's research can aid current healthcare practices beyond drug selection.

One benefit of identifying biomarkers linked to disease subgroups is a possibility to use them to aid post-treatment monitoring of diseases such as AML. As Clinician 1 explained,

> We could also use [molecular information] for tracing minimal residual disease. This has meaning in some diseases, for others' no. For example, in acute leukaemia, it is very important that we would find a tracer marker for the minimal residual disease. In AML we don't have that with the current methods so maybe we could find new gene mutations

> with this [research]. Then we could analyse these numbers more precisely, with some PCR method, which would tell us how much minimal residual disease there is. Maybe we could start using these kinds of [applications] already in the near future.
>
> (Clinician 1, my translation)

Minimal residual disease (MRD) refers to the cancerous cells that remain in the body after treatment. In medicine, it is important to be able to track the MRD and to count the number of cancerous cells in order to choose the best follow-up treatment option. In AML, this has been difficult to do, as there has been no effective marker to indicate the level of MRD in the body owing to the molecular heterogeneity of AML.[296] Thus, subcategorising molecular profiles in AML could help in planning methods to efficiently detect MRD by finding biomarkers that can help to plan the forthcoming treatment options.

In addition, disease risk profiles based on knowledge of mutations linked with the disease could help in diagnosing the disease. As Clinician 1 stated when commenting on FIMM's research's benefit to today's clinical practices, "maybe in risk-rating as that actually comes before [applying the treatment]. When we find a new cancer gene, the first benefit to patients is probably the development of different kinds of risk-ratings plus of course that some genes show higher risk." Defining risk genes, a practice that has gained a lot of media coverage in cases of the breast cancer genes BRCA1 and BRCA2, could then help in actual diagnostic and preventive practices.[297]

Identifying biomarkers that show a risk of developing diseases was also at the heart of Hood's lecture at the University of Helsinki in 2014, when he presented the Hundred Person Wellness Project (P100). The significance of biomarkers for this pilot study is evident in the report of the project, published in August 2017. The project was based on collecting diverse longitudinal data—in this case, for nine months. This data included "whole genome sequences;

[296] Grimwade & Freeman 2014, 3345.

[297] Ability of detecting risk genes has also introduced commercial gene-testing products that show individual susceptibility to diseases such as breast cancer. This has led to new discussions of the relation between public healthcare and private commercial interests and individuals' possibilities to control their own health. See Sándor 2018.

clinical tests, metabolomes, proteomes, and microbiomes at 3-month intervals; and frequent activity measurements (i.e., wearing a Fitbit)."[298] Studying this data, the researchers formed predictions, based on known measurable biomarkers, for example, for cardiovascular diseases, on individuals' probability of getting a certain disease in the future. This information was then discussed with the personal health coach to consider what kinds of lifestyle changes could help to modify "markers of known clinical significance and/or compensating for genetic predispositions."[299] While being customised to each person's situation, "these individual recommendations typically fell into one of several major categories: diet, exercise, stress management, dietary supplements, or physician referral, as relevant for each participant."[300] By connecting patient data with the knowledge of existing biomarkers in the context of biological networks, as concluded in the publication, this study was able to identify personalised risk factors for the participants as well as to locate possible new biomarkers.[301] Thus, it shows well a larger requisite of such projects: people's active participation. Participation, one of the Ps in Hood's vision of P4 medicine, is then needed not only for obtaining clinical relevance, but also for developing the study's predictive measures.

As mentioned at the beginning of this chapter, the P100 project that Hood described in his lecture received mixed responses from FIMM's researchers. This works as a good reminder that larger aims connected to P4 medicine can seem rather distant to researchers working on more precise research questions on disease mechanisms. While FIMM's researchers are dedicated to advancing personalised approaches in cancer treatment, and larger goals are considered in funding applications, most of their work is not actively related to the broader changes often associated with systems medicine initiatives. At the moment, FIMM's research is working towards personalised and precision medicine by focusing on drug development, but

[298] Price et al. 2017, 747. Fitbit is a device that records wearers' daily activity and sleep.
[299] Ibid., 752.
[300] Ibid., 753.
[301] Ibid, 754–755.

less on preventive and participatory medicine, thus, missing two Ps from Hood's envisioned P4 medicine. This might help to explain why FIMM's researchers had many critical remarks after Hood's lecture. However, this does not mean that FIMM's research should be seen separate from these broader aims of P4 medicine. Instead, it is important to question how FIMM's current research is seen to support these future aims advocated by Hood. To further consider how FIMM's research is connected to the aims outlined by Hood, I will investigate how FIMM's research is a part of, what Helga Nowotny calls, "genomic revolution".

2. Big Data, Genomic Revolution, and Path Towards Personalised Medicine

In her book, *The Cunning of Uncertainty* (2016), Nowotny considers social concerns brought by science's intimate connection to uncertainty. She analyses changes happening when big data approaches are brought into scientific research and increasingly to decision-making processes. One topic she emphasises in her book is how this is seen to influence the future of healthcare. She notes that to understand how big data is altering decision-making practices, one must cease to see understanding of causality as the main basis for decisions. Instead, big data-derived decisions are based on probabilities predicted through correlations. As Nowotny writes, "[t]he question is no longer how systems behave or how to make predictions for the properties of a system, but how to ask for the probability distribution of the properties that change with the system."[302] As Viktor Mayer-Schönberger and Kenneth Cukier put it in their book *Big Data* (2013), "society will need to shed some of its obsession for causality in exchange for simple correlations: not knowing *why* but only *what*."[303] In other words, decisions can be derived from predictive probability calculations based on enormous data sets, finding out what kind of action

[302] Nowotny 2016, 42.
[303] Mayer-Schönberger & Cukier 2013, 7.

would be most fruitful considering the earlier treatment outcomes. As these correlation studies would be done by a computer assessing existing data, people could not fully understand why the said prediction takes place. This, Mayer-Schönberger and Cukier continue, "overturns centuries of established practices and challenges our most basic understanding of how to make decisions and comprehend reality."[304]

Examples of big data approaches usually come from commercial venues, such as Amazon's ability to predict which books you might want to order or Netflix's suggestions for things to watch next. These suggestions are based on probability calculations that consider both what you have previously bought/watched and what others buying/watching similar things have bought/watched. In healthcare, this future vision goes as far as imagining decision making based on computer *in silico* models of human cells and human bodies as the basis for predictive probability calculations.[305] As defined by Fischer et al., "The hope is that with enough data, systems biology will be able to generate a computer algorithm that is able to predict how the body will respond to inputs, without actually understanding the mechanisms of the body. For such a model, the internal working of the body would remain a 'black box'."[306] As suggested by the P100 project, led by Hood, the basis for these probability calculations would be the continuously increasing amount of followed-up personal data from which the best-possible treatment solutions could be predicted based on earlier treatment outcomes. It is no wonder, then, that Nowotny uses the term, 'genomic revolution' to describe transformations connected to big data approaches in medicine as "in science, revolution usually means a new scientific way of seeing the world, undermining certainties that are taken for granted and opening exciting paths for more and better understanding that comes from manipulation and intervention."[307]

[304] Ibid.
[305] See Corander et al. 2012 and Pavelić et al. 2016.
[306] Fischer et al. 2016, 6.
[307] Nowotny 2016, 98.

These are, still, future visions for personalised medicine. One reason why such approaches are difficult to implement in medical decision making is that while big data can enable predictive probability calculations, they do not just appear from it. As Nowotny emphasises, "[b]ig data and the simulation models they feed allow us to see further, but as neither data nor models speak for themselves, they need careful interpretation. The uncertainties that reside in them must scrupulously be put into context."[308] The difficulties embedded in this requirement were clear also to FIMM's researchers. As Researcher 13 emphasised,

> In systems biology, people often speak of data integration and how that will solve all the problems. That would, indeed, be fantastic. However, that is often just an unsubstituted claim and the organisation and upkeep of data is hard work. (…) It doesn't happen so that you just decide that "I will integrate these like this". But, of course, that is the aim and in the best-case scenario we could use all these exquisite omics-methods and integrate them with the data and then get the results into plain language that we could give to the clinician. That is the reason behind our work.
>
> (Researcher 13, my translation)

These comments bring forth two important prerequisites that need to be examined to understand challenges that systems medicine still has to overcome. Firstly, for the increasing data to benefit treatment predictions, they have to feed existing simulation models. In other words, one needs to first establish a simulation model. Secondly, to benefit the development of such simulation, outcomes of the predictions need to be tested to formulate feedback that can refine the simulation.

2.1. Forming simulations

The systems medicine approach requires a basis from which to integrate and interpret available data in a meaningful way. In other words, to create measurements according to which the treatment options can be planned and their success evaluated. As Corander et al. write in their article "Rocky Road to Personalized Medicine" (2012), "the in silico prediction models and the

[308] Ibid., 9.

related systems biology are expected to evolve gradually through feedback and refinement on the basis of statistical modelling of the predictions tested against real outcomes from individual patients."[309] In other words, treatment predictions would become more rigorous with the assessment of each following treatment and, thus, future predictions would develop to be more and more precise.

This requires more research on possible measurable biological indications and disease-network analysis, which can then be assessed and developed in comparison to treatment outcomes. To get to the point of testing the functionality of known biomarkers for different diseases, these biomarkers have to be first identified. As Corander et al. write, "[p]erhaps the most promising currently considered initial step towards genuine personalized medicine is stratified medicine."[310] Notably, this initial step also connects FIMM's research to the broader aims of personalised medicine as in stratified medicine "the key task is to use multiple biomarkers jointly to identify subpopulations of patients who differ in terms of their disease traits or treatment outcomes."[311] As noted in Chapter 3, this is what FIMM's researchers strive to do. Calculating correlations between multiple disease biomarkers and analysing their functionality through network analysis was also the basis for the P100 pilot study, which Hood sees as "the first real-world test of the 'P4 medicine' paradigm."[312]

In the P100 pilot study, the aim was to optimise participants' wellness through health coaching based to the information gained from blood, saliva, excrement, and urine samples, as well as lifestyle information provided by the participants, from which different markers were measured. For example, stool samples were used to examine gut microbiomes with the help of 16s rRNA sequencing and a whole genome sequence analysis was done for each participant based on their blood samples and in total 130 different disease risks and quantitative traits,

[309] Corander et al. 2012, 110.
[310] Ibid.
[311] Ibid.
[312] Hood et al. 2015, 1.

based on previous studies, were calculated.[313] To connect these biomarkers to individualised risk probabilities, this information was analysed together with network data, in other words, models of how biological functions operate in multiple, related, levels of networks in human's biological systems. As Hood writes in his article "Systems Biology and P4 Medicine" (2013), "Biological organisms consist of interconnected biological networks of networks, both within and between cells. To truly understand complex biological phenomena, they must be studied in the context of this network complexity."[314] While biomarkers, thus, can help to locate and measure potential risk factors, their individual relevance, and inter-connectedness, can only be calculated through the connection with network analysis.[315] This network analysis, then, helped to form a sense of "communities of related analytes associated with physiology and disease"[316] which also helped to design the health coaching aimed to reduce the risk identified with these biomarkers, noting that these biomarkers showed a different kind of risk for each participant when connected to other biomarkers. The project, hence, helped to see whether certain lifestyle changes altered the biomarkers that were seen to contain personal risk. In addition, the data gained during the project brought forth possible new biomarker identifications that can be further studied.[317]

However, it is questionable whether the P100 pilot project can be seen to represent systems medicine as the kind of big data approach envisioned before. This is because, in the P100 project, probabilities were still based on a set of known biomarkers and, thus, they were searched from the data rather than predicted from it. Hence, also the health coach suggestions were based on "lifestyle changes that have been previously demonstrated to produce improvements in that marker," though all guidance was individually adjusted.[318] According to

[313] Price et al. 2017, 474.
[314] Hood 2013, 5.
[315] In the P100 study, two correlation networks were formed, which were adjusted according to age and gender.
[316] Price et al. 2017, 747.
[317] Ibid., 754.
[318] Ibid., 752.

this evaluation, the P100 study still relies on the stratified medicine approach, whereas in truly personalised medicine, "each treatment group consists of a single individual."[319]

Yet, Hood's project shows well how personalised medicine requires these kinds of studies in order to emerge. This, Corander et al. write, is because "it is impossible to learn to predict from data of a single patient before treatment outcomes have been measured."[320] In other words, as Nowotny's earlier statement emphasised, in the big data approach, the predictions need to be still interpreted in a context where feedback can be fed for the model based on the success of these interpretations. In the ultimate stage of personalised medicine, predictions are made from data from a single individual, as imagined by Corander et al.,

> dense follow-up data will be an inevitable prerequisite for reliable inference and predictions. (…) In this way, each individual is providing his or her own control measurement, thus enabling individual level predictions of the disease progression and relapse, something that is not obtained on the basis of the cross-sectional case-control designs.[321]

However, Corander et al. highlight that to reach this level of computer-based predictive models, "it is necessary to consider the intermediate steps where statistical models are built for the purposes of both prediction and systems level understanding, from current and emerging data."[322] What is more, testing these kinds of models, which is needed to adjust the models through feedback, also has ethical and legal constraints.

2.2.Testing Simulations

In order for the big data approach in personalised medicine to develop, the *in silico* models that function as the basis for treatment outcome predictions, need to be tested in real-life. This creates a methodological challenge as Corander et al. note, "[g]iven that several sources of

[319] Corander et al. 2012, 110. A similar point about the difference between stratified medicine and, truly, personalised medicine has been made in Langkafel 2015, 27.
[320] Ibid.
[321] Ibid.
[322] Ibid., 112.

uncertain evidence will be needed in making the predictions, it may be difficult to justify making treatment choices based on predictions of the abstract models, no matter how well interpretable they are."[323] In the P100 pilot project, this ethical dilemma was less apparent as Hood et al. point out in the description of the project,

> The project's focus on wellness means that many of the findings communicated are actionable in terms of improvements to nutrition, exercise, stress management or compliance with existing medical prescriptions. These actions are thus safe, generally low-cost and consistent with practices well known to promote overall optimization of health and wellbeing.[324]

In the P100 project, then, it was possible to test how the lifestyle changes affected the measured biomarkers, as these changes were seen as harmless because they were in accordance with existing ideals for enhancing wellbeing. To the contrary, a similar statement could not be made in case of clinical situations, where *in silico* models could suggest that a disease should be treated with an unconventional method, such as an unapproved drug.

Corander et al. conclude by stating that one way of furthering stratified medicine approaches in healthcare that can lead to personalised medicine is by participating in drug development. They write that "the use of the models can therefore perhaps be most easily justified in drug repositioning, when using already approved drugs."[325] In other words, connecting basic research with drug development can help to prove that *in silico* models can be of use when predicting treatment outcomes. Moreover, as is here mentioned in relation to off-label drug cases, drug trials also give researchers a possibility to assess the functionality of their predictions and modify their models based on this information. As has been underlined in this chapter (see subsection 1.1), predicting how new or off-label drugs function in a patient subgroup is anything but simple and can only be done with patients who have no standard treatment options left. These cases, as suggested above, can be more easily justified in the

[323] Ibid., 113.
[324] Hood et al. 2015, 3.
[325] Corander et al. 2012, 113.

research. This functionality testing, as has been emphasised, is only possible through close collaboration with the clinicians that take the final responsibility in deciding whether the interpretations made from DSRT platform results can be taken back to clinical treatment or with pharmaceutical companies, which can formulate new clinical trials.

This conclusion made by Corander et al. is hardly surprising considering that half of the authors of the piece were working at FIMM at the time of the publication. This is not to say that seeing the development of precision drugs as a manner of validation of systems medicine approaches would be rare in discussions around developing personalised medicine.[326] Instead, what this helps to pinpoint is the fact that FIMM's research, with its focus on drug development in the ISM program, should be viewed together with the broader future aims connected to personalised medicine. However, as noted before, many of the goals connected with personalised medicine are still distant to FIMM's researchers as their focus is largely on understanding basic disease mechanisms, in other words, trying to formulate analyses of the causal functions in disease pathways. When considering future scenarios linked to personalised systems medicine, it is no wonder that these plans can seem distant for many researchers at FIMM. These visions have also brought forth ethical dilemmas in the future of systems medicine research, such as the possibility of over-diagnosing and false positive results, additional healthcare costs, and increasing global inequalities in healthcare.[327]

Fischer et al. note ethical dilemmas related to envisioned clinical practices in personalised systems medicine in their article, published in 2016. They note that the top-down model in systems medicine, which would provide treatment predictions from the correlations found from a large data set,

> provides clinicians with a computer algorithm, but that algorithm represents the patient's body as a black box. It is not based on mechanistic science, and it is not based on clinical research. It simply takes the patient's data, and generates an output. Neither clinicians nor patients have a way to evaluate its predictions. We are faced with the choice of following

[326] See, for example, Pavelić et al. 2016, 7 and Becker 2016, 23.
[327] See, for example, Blanchard 2016; Green & Vogt 2016; and Vogt et al. 2016.

> its predictions, or ignoring them. But this choice is arbitrary, and based purely on confidence in the black box.[328]

Fischer et al. are critical towards the lack of accountability that doctors have in this kind of situation. This example raises the question of interpretability of big data-generated treatment predictions and strongly shows the opposition towards computer-simulated treatment outcome calculations where the doctor's role in treatment prediction is considered insignificant. This, they envision, can lead to even more concerning possibilities where the prediction would take into consideration also whether it would be economically sensible to terminate the treatment.[329] These scenarios, as Fischer et al. note, do not describe current practices but imagine ethical concerns that would take place if personalised systems medicine would develop as planned. Still, Fischer et al. maintain the value of top-down approaches in basic research as they can help in formulating hypotheses.[330] As shown in Chapter 3, in FIMM's research the *in silico* models have this kind of role in research as computational models are developed together with cell biology models.

While Fischer et al.'s article is a strong reminder of the need to consider future applications of the systems medicine approach, these horror scenarios do little in showing how mechanistic causal explanations are still very much attached to personalised systems medicine projects, as they still function at the level of stratified medicine. To take stratified medicine seriously as an "intermediate step", as Corander et al. call current practices, requires considering how mechanistic understanding of diseases, or "bottom-up simulations" as Fischer et al. call them, are connected to top-down correlation studies. While the future aims of personalised medicine might well be invested with the aims of producing functional top-down big data approaches without the need to support decision making on the causal models of the related biological phenomena, at this "intermediate" stage, the causal explanations are still creating the

[328] Fischer et al. 2016, 6.
[329] Ibid., 8.
[330] Ibid., 7.

basis for interpretations. This stage is clear when considering the current clinical applications of systems medicine research at FIMM: while *in silico* models are used to predict treatment outcomes based on DSRT studies, the clinical relevance of the predictions is always assessed by the collaborating clinicians. In these decisions, as has been argued in subsection 1.1, clinicians have to take into consideration information of the patient beyond their molecular profile.

As highlighted in Chapter 2, this process of bringing the knowledge of basic disease mechanisms back to the clinic is where known gender differences might influence treatment decisions. Thus, gender can also be a useful tool in further investigating the changes envisioned in the systems medicine initiatives.

3. Comparing Gender Medicine and Personalised Medicine

One of the criticisms towards personalised medicine initiatives is that their 'holistic' view on human health is based only on measurable biological parameters. Vogt et al. state that P4 systems medicine (P4SM) "seems to adhere to the machine metaphor of life. Mechanistic explanations and predictive power are main goals."[331] Although systems medicine literature highlights the need to study human health as an outcome of a complex interplay between different levels of networks in and of the body, including the body's relation to individuals' actions and their environment, Vogt et al. note that in practice, "operationalizing and modelling complex personal and social factors is harder and has a much lower priority in current P4SM research than the molecular level."[332] This, according to them, leads to a reductionist view of human health and drug development that then becomes the main focus of systems medicine

[331] Vogt et al. 2016, 312–313.
[332] Ibid., 318.

research.[333] Vogt et al.'s criticism can also help to explain why systems medicine researchers at FIMM do not consider gender differences in their analysis. At the moment, FIMM's work is focused on studying basic disease mechanisms, trying to identify patient subgroups based on their molecular-level differences. However, as noted in Chapter 2, gender is a possibly relevant analytical tool when considering how molecular-level information is brought back to clinical decision making or to the planning of preventative measures. Thus, in order to grasp how gender analysis could benefit personalised medicine initiatives, it is necessary to examine how gender medicine and personalised medicine approaches differ.

3.1. Gendered Criticism Towards the Personalised Medicine Approach

The focus on molecular-level measurements has been one of the gender medicine's critiques towards personalised medicine approach. As Vera Regitz-Zagrosek together with Ute Seeland write in the introduction of the book *Sex and Gender Differences in Pharmacology* (2012), gender medicine research initiatives should be considered together with personalised medicine approaches,

> Personalized medicine cannot replace gender-based medicine. Large databases reveal that gender remains an independent risk factor after ethnicity, age, comorbidities, and scored risk factors that have been taken into account. Some genetic variants carry a different risk in women and men. The sociocultural dimension of gender integrating lifestyle, environment, stress, and other variables cannot be replaced by a sum of biological parameters. Because of this prominent role of gender, clinical care algorithms must include gender-based assessment.[334]

There are two important remarks made in this statement about the difference between gender medicine and personalised medicine initiatives.

Firstly, gender is one of the big risk factors that should be included into calculations concerning clinical care. While knowledge about gender differences in diseases is becoming

[333] Ibid.
[334] Regitz-Zagrosek & Seeland 2012, 4.

commonplace, they are still surprisingly undermined and understudied in clinical research.[335] However, as emphasised in Chapter 2, even if gender is used as a risk factor, as was seen also in the P100 study,[336] this consideration rarely goes as far as to consider the basis for shown gender differences. Rather, examination of gender differences can be seen as "crude stratification"[337] as it often only shows that there is a disease risk connected to gender. Seen this way, it is understandable why FIMM's researchers working on systems medicine projects saw studies of gender differences distant from their daily work as "[s]uch population based studies in general fail to account for heterogeneity in the target population".[338]

However, further discussions with FIMM's researchers showed that even though gendered analysis is not currently used in their research, they saw possibilities to use it to develop personalised medicine research. This became especially clear in my interview with Researcher 9 (the leader of Group F) and Researcher 16 (from Group C), both women, who were in charge of coordinating FIMM's involvement in the LIBRA project. As FIMM's newsletter, published on their webpage in November 20th, 2015, mentions, the project is "aimed to evaluate the current status of gender equality in the EU-LIFE institutes and implement innovative actions to increase representation and participation of women in leadership positions in life sciences in Europe as well as raise scientific excellence by *including sex and gender dimension in research*."[339] As the project was launched during my fieldwork in 2014, I returned to FIMM in May 2017 to question how the project had evolved. This gave me also an apt opportunity to ask more about the need for the gender aspect in systems medicine research.

When I asked whether a gendered approach could benefit systems medicine research, both researchers readily declared its potential benefits. However, my follow-up question of how

[335] As is noted in an article examining how gender differences are present in cardiovascular diseases, "[t]here is a lot of published knowledge on S&G differences but the awareness is low." See Regitz-Zagrosek et al. 2016, 25.
[336] Price et al. 2017, 749.
[337] Corander et al. 2012, 109.
[338] Ibid.
[339] <https://www.fimm.fi/en/news/1448020071> [Accessed 25.2.2018] My emphasis.

gender could be beneficial produced no such immediate answers. Still, Researcher 16 replied, "in the concept of personalised medicine, we always talk about the individual and how the individual responds and what's the molecular profile of an individual but perhaps taking into account the sex differences, those individuals could also contribute to those different responses and that might help stratify patient groups already more than now." Thus viewed, acknowledging gender differences could benefit the current state of the research which is at the level of stratified medicine, as discussed in prior parts of this chapter. However, Researcher 16 later continued to consider possible obstacles for acknowledging gender differences in their research:

> Maybe our numbers aren't quite big enough yet, too. And the systems medicine side, too. Until we have really enough patients that are of one disease, of one kind of different stratified group of that disease, of one gender of that stratified group disease. (…) I think right now in personalised medicine side of things, people are just super excited when they get *a* sample—*a* patient sample. So it's maybe not yet coming to their minds.
>
> (Researcher 16)

While the number of patient samples in rare diseases such as AML studied at FIMM might make it difficult to obtain enough data for gendered analysis, my interview with Researcher 9 and Researcher 16 left me with a sense that gendered analysis could gain a more prominent role in systems medicine research in the future.[340]

Increasing clinical collaboration of institutes such as FIMM could stress the value and relevance of gendered stratification of patients. As Researcher 8 noted at the end of our interview when discussing the role of gender analysis in their work,

> We have started at least to keep an eye on it, to include it in our analysis and we have one project with a pharmaceutical company where—one of the drug candidates they had—we need to keep an eye on gender in it because … certain genetic factors seem to be travelling from men and not from women or vice versa so that's our first attempt to really start looking at that. (…) I think we genuinely have not, initially have not, included [gender] in the analysis when we're looking for different markers so it's been a more simple-minded focus on what mutations do we have and what other molecular profiles we have. But ultimately we want to go back to clinical features and this company project brought up a good point. So it's in there but we haven't focused on it.

[340] I will return to the possible ways to incorporate gender in research in Chapter 5.

(Researcher 8)

This example shows that understanding the basis for gender differences becomes relevant for FIMM's research when they encounter gendered differences in drug treatment outcomes. FIMM's systems medicine research is still on the level of stratified medicine and drug development rather than developing risk assessments to benefit disease prevention discussed in Regitz-Zagrosek and Seeland's comparison between personalised medicine and gender medicine. Still, it is important to underline that studying gendered differences in diseases could be used as one way to develop systems medicine research towards more effective personalised medicine. Thus viewed, the juxtaposition between the two fields seems unnecessary.

However, the second emphasis in Regitz-Zagrosek and Seeland's statement complicates this vision of gender-based medical analysis. By highlighting that gender-based research needs to consider both biological and sociocultural bases as a possible explanation behind gender differences in diseases, they emphasise the need not only to account for gender differences in research but to actively study the reasons behind such variation. Here, the differentiation between gender medicine and personalised medicine relies on the same criticism as made by Vogt et al.: personalised medicine relies strongly on biological parameters and, hence, fails to account for the sociocultural aspect of disease emergence and treatment. As the study of gender differences would require the possibility to consider both the biological, such as hormones, and the sociocultural aspects, such as lifestyle and nutrition—not to mention that these two sides also influence one another—studying reasons behind gender differences needs to go beyond biological parameters.

Nevertheless, when reading through personalised medicine literature, it is obvious that there is a wish to better include considerations of environmental factors to personalised medicine research projects. Therefore, personalised medicine initiatives seem to share a similar wish with gender medicine that future research projects would better consider gene-

environment interactions. In what follows, I will first illustrate this point with the help of the discussion around biobank legislation. Through this example I will show that personalised medicine initiatives aim to integrate more and more additional information to the biological samples collected at biobanks. This wish has brought forward a lot of discussion over data protection and data accessibility as this kind of information is interesting also for private companies.

3.2. Biology as Information in the Example of Biobanks

In his article from 2013, Hood makes a bold statement: "Biology can be defined as an informational science."[341] He goes on to separate between two types of information in biological systems: "the digital information of the genome and the environmental information which consists of signals brought from outside of the genome."[342] In order for personalised medicine to create an adequate consideration of health, both of these information types need to be included into the research. This requirement shows a bigger change that has been taking place in biomedical research during the last few decades.

As noted by Geraldine Fobelets and Herman Nys, by the beginning of the 21st century, the focus on biomedical research had shifted towards studying how "most genetic diseases are caused by a complex interplay of many factors, both genetic and environmental."[343] While studying this complexity of biological organisms has been made possible by the increased opportunities of employing mathematical and computational analysis into medical research, it has brought forward an issue of how to efficiently collect, store, and distribute patient

[341] Hood 2013, 4.
[342] Ibid.
[343] Fobelets & Nys 2009, 20.

information and samples that are needed for such research. These challenges have been faced with the aim of formulating consistent biobank legislation.[344]

As Barbara Parodi notes, the term 'biobanks' can be confusing as there are different kinds of biological sample collections, some containing, for example, tissues from animals, plants, or bacteria. However, she notes that "a biobank typically handles human biospecimens—such as tissue, blood, urine—and information pertaining to the donors: demography and lifestyle, history of present illness, treatment and clinical outcomes."[345] While such data has been gathered for centuries, the current ethical and legal debates—and the need to define "biobanks" —comes from the wish to standardise sample collecting methodologies, outline who can access the samples and the data, and how they can access it. To formulate national and European standards on collecting, protecting and distributing human biological material and connected information is a drastic change in previous data-exchange practices as "traditionally, researchers have held onto their sample collections like treasure, and have only granted access to other researchers in exchange for something of benefit to them."[346] As noted by some researchers at FIMM, whose expertise was on mathematical modelling of biological data, this traditional way of handling data sharing can create a lot of difficulties for them when they ask to obtain collection data, as they have little to offer in return. Thus, changing practices in biomedical research have also brought forth needs to alter data-sharing habits. Setting up biobanks are not only necessary for researchers outside of conventional biological research but from the researchers' point of view, biobanks are essential for enabling big data-derived biomedical research as they allow scientists, firstly, to access more suitable samples. This is especially important when studying rare diseases where it might be challenging to collect enough patient data to study and prove research hypotheses. Secondly, biobanks enable

[344] See, for example, Eero Vuorio's account of the challenges connected to the aims of forming biobank collaboration in Europe. Vuorio 2017.
[345] Parodi 2015, 15.
[346] Silvola 2012, 288.

researchers to share their expertise in collecting sample data, which can then aid the sharing of data.[347]

In Finland, the new Finnish biobank law was introduced in 2013 and it has made the issue of accessibility of patient data more prevalent. The law established the first standardised protocol for the functions of biobanks in Finland. One of the biggest changes to previous practices is that patient consent is now collected only once when the first sample is taken and without specifying the research in which the sample might be used. One of the reasons why Finland has been considered a good country for molecular research is people's willingness to participate in sample collections. Therefore, current biobanks contain many collections that have been collected over the years in individual disease studies and national health assessments. Before, however, this information was owned by the people who conducted the research and it was only accessible by collaborating with the collectors. With the new biobank law, these collections are owned by the biobanks, which can be publicly or privately owned.[348] This means that this information is potentially accessible to anyone, including pharmaceutical companies and other industries, that have applied, and paid for, the use of the data.

When considering researchers' abilities to analyse gene-environment interactions in disease aetiology, progression and treatment, setting up standards for data collecting, handling, and sharing is essential. It is important to note that lifestyle data has been collected in medical research before and, thus, is not a new way to approach the study of diseases. However, considering the increasing value given to data-centric approaches, we are now facing the question of whether such data should be collected outside of particular research projects and be accessible for broader research interests. As Christian Lenk, Judit Sándor, and Bert Gordign note, "a future scenario is emerging in which there is always existing data stored on every

[347] Shickle & Griffin 2009, 1.
[348] The biobank law can be read from: <http://www.finlex.fi/fi/laki/alkup/2012/20120688#Pidm1757072> [Accessed November 20, 2016].

citizen in many areas of life (i.e. social life, social contacts, financial situations, professional backgrounds, living and working conditions, health, and also the genetic outfit) by public and private players."[349]

Furthermore, in regards to biobank's operation, it is important to ask what are the limits not only in collecting but also in moving such data. As Lenk, Sándor and Gordijn note, "if a person or institution had the opportunity to combine and use this data altogether, fundamentally new dimensions of knowledge about a person or a larger group of people might well occur."[350] While this might then bring forth interesting medical research, also in the studies of gendered differences, it also raises legal and ethical questions of producing and moving such data. These questions relate to broader concerns over individual privacy and concerns over who can access such data. While data-protection plans are often focused on guaranteeing the anonymity of patients whose data are used in research, recent examples show that, especially in the case of genomic data, such ultimate anonymity is a shallow promise.[351]

The legal, ethical and political discussions around biobanks show well the challenges of integrating broader private information into medical research. This can partly explain why there is a focus on molecular markers in systems medicine research as information on people's lifestyle has not been included in previous data collections.[352] However, ongoing attempts to clarify and extend data access for research purposes indicate the wish to cover gene-

[349] Lenk et al. 2011, 4.
[350] Ibid.
[351] In 2013 two studies challenged the idea of anonymity in biological sample data. Three scholars, Latanya Sweeney, Akua Abu, and Julia Winn from Harvard showed that they were able to identify people by name from anonymised data collected for the Personal Genome Project. Another such study was made, with even less data, by Yaniv Erlich from the data collected for the 1000 Genomes Project. This was possible because, even though not connected to these particular studies, some participants' genome had been recorded online in other instances, such as when buying a gene test to study one's ancestry. Companies, such as 23andMe, can also sell this data to other parties. These cases have come to show how promising full anonymity for biobank data is impossible. Because of this, some go as far as to suggest that the data-sharing discussion should not be based on questioning how to protect individuals' privacy but how to support data sharing as an act of communal solidarity. See Prainsack & Buyx 2017.
[352] Another explanation could be difficulties in gaining reliable information about people's nutrition, exercise and other lifestyle factors. Even in the P100 pilot project this was challenging to do as participants' "compliance with quantified self-tracking was relatively low." Price et al. 2017, 749.

environment interactions in big data medical approaches. This access is needed as, although the future vision of personalised medicine holds that data would be gathered continuously from the individual to assure their personalised risk probabilities, at the current level of stratified medicine, *in silico* models still need to integrate such data as a part of their predictions.

This is an aim shared by both systems medicine and gender medicine initiatives, as both emphasise the need to more fully account for the possible reasons behind individual differences. Gender-focused approaches could be used to further clarify the meaning behind gendered risk calculations. Seen this way, gender-based focus could support personalised approaches in medical research. As reminded by Nowotny,

> The probabilities derived from comparing an individual's unique genomic make-up with that of a growing number of other individuals are based on the interpretations derived from many additional studies that link phenotype with genotype. The old model of looking for causes has not vanished because symptoms have become manifest, nor have disease, suffering and death.[353]

However, seeing gendered analysis only as a tool for advancing personalised medicine could easily reduce its research relevance to an "intermediate" step, or as another example of the stratified medicine approach. To say this would be to ignore a more foundational difference between gender medicine and systems medicine approaches: a difference on imagining what should be prevented and how. In the following part, I will show that while both the gender medicine and personalised medicine initiatives share the wish to consider gene-environment interactions in disease emergence and treatment, they have a different focus when it comes to the imagined ways of preventing disease emergence.

3.3. Prevention as Population Based vs. Individual Control

At the end of our interview in 2014, the leader of FIMM described the newest project, which they were applying funding for. He encapsulated this project that he later, at the end of Hood's

[353] Nowotny 2016, 101.

presentation in Helsinki, likened to the 100P study, by comparing its aims to car service. When something is wrong with your car, he explained, you get a warning signal and then you take it to the car service. This is based on a continuous monitoring of the car system, which is then able to alarm you if something goes wrong. He ended the metaphor by stating that we, currently, do not have this kind of monitoring in our lives. What projects such as the 100P study aim to do is to make this monitoring system available for individuals, who could then act on these warning signals. Based on this example, it can be understood why one of the Ps in P4 medicine stands for 'participation'. While it might be the car service, or individual health coach, that tells you what needs to be done to avoid engine, or wellness, failure, it is up to the individual to control their own health. Thus, active participation is not only needed for data collection but preventing diseases is only actionable if the prediction generated from this data is affecting individuals' way of living.

In order to grasp the difference that this approach brings between gender medicine and personalised medicine, it is important to note that here, as well as in P4 medicine initiatives more broadly, the emphasis is on prevention directed towards healthy individuals. Compared to the previous section, which highlighted how the personalised approach shares the gender medicine's goal to better account for gene-environment interactions in research, in relation to prevention, there is a difference in emphasis between population scale preventive measures in gender medicine and individual-focused personalised medicine.

In their article "Personalizing Medicine: Disease Prevention in silico and in socio" (2016), Sara Green and Henrik Vogt listed problems that might arise if healthcare was organised around optimising individual wellness, as imagined by Hood and other proponents of systems medicine. First of all, they challenge the assumption that the systems medicine approach would necessarily cut healthcare costs in the long run. They further raise questions of possible individual harm caused by false positive diagnoses. Moreover, they question whether

individuals would want to participate in such preventive actions and act accordingly. This assumption, they criticise, is based on a presumption that "the goals inherent in P4 medicine are perfectly aligned with other goals in personal life and society."[354] Owing to these reasons, they call for caution when thinking that P4 medicine approaches should replace older healthcare models. They conclude the article by stating that,

> The shift of focus from culturally or structurally related causes of diseases (socio-economic factors, pollution, urban planning) to individualized preventive strategies must be backed up by evidence that this can improve health outcomes. Thus, the issue at stake is not only whether P4 strategies will give useful results, but also whether resources will be wasted that could be better spent elsewhere and whether *less medicine* in some contexts means *more health*.[355]

This statement brings forth an important social condition that has been viewed as one of the benefits of personalised medicine approaches in preventive healthcare: that it would help to reduce the healthcare costs in the long run. This being the case, a follow-up question arises: where to get the money to support its initial phases before (expected) decrease in costs? As Green and Vogt suggest, this can lead to a situation where other forms of prevention, such as gender-based ones, become less emphasised in prevention plans. In an ideal situation, these two approaches could benefit one another. Yet, many of the visualisations of the personalised medicine future seem to put society's role mainly as something that enables individuals to control their health. For example, when Peter Langkafel considers, in his introduction to "Big Data in Medical Science and Healthcare Management" (2015), how big data could help to support our information regarding the importance of exercise, the role of society in investing in preventive care would be to invest on bicycle paths to help people cycle more.[356] While these kinds of investment could definitely benefit people's wellbeing, it is notable that in this scenario, the emphasis is again on individuals' responsibility to, then, cycle. Vogt et al. note that when prevention is focused on individual's own control and responsibility "[p]atients may

[354] Green & Vogt 2016, 126.
[355] Ibid., 131.
[356] Langkafel 2015, 7.

become more active, but their goals are still defined by the agents behind P4SM."[357] Thus, one could ask whether similar concerns over people's nutrition could lead to the state's control over nutrition habits, for example, through tighter taxation, or just tougher statements over people's own responsibilities over their eating habits. Gender-based research could offer different kinds of prevention plans because it can be caused by a myriad of factors, especially if connected to consideration about age, class, race, and other differences that can influence disease aetiology in different population subgroups. The question then remains: how do we keep these levels of questions as a part of scientifically, medically, and politically relevant questions? This problem is central to the feminist engagement with systems medicine research, which I will develop more in the next chapter.

In this chapter, I have examined the relationship between personalised medicine initiatives and FIMM's research. I have shown that FIMM's research is largely based on studying basic disease mechanisms and its translational value is mostly in its connection to drug development. However, in its focus on biomarker identification and disease networks, its stratified medicine approach can be seen to support the development of personalised medicine. Through showing how explanation models are still at the centre of the pilot project progressing personalised medicine, I have called for a need to see how personalised medicine projects are still in their "intermediate steps" where, for example, a gender-based research approach could benefit the prediction accuracy of disease treatment. However, when it comes to prevention, a gender-based approach offers a different kind of emphasis on its actionable framework when thinking of preventive social measures in contrast to an individual's control over their own health. This, I conclude, can help to better envision what feminist engagement with systems medicine research could look like.

[357] Vogt et al. 2016, 319.

Chapter 5

Forming Feminist Engagement with Systems Medicine

In this final chapter, my aim is to return to the question of what it would mean to form feminist engagement with systems medicine. As highlighted in Chapter 1, this is a question that requires focus both on the epistemological practices in current research and contextualising current systems medicine research as part of broader changes imagined together with personalised medicine. In the previous chapters, I have aimed to engage with systems medicine research. I have done this by examining how a systems biology approach is applied to medical research in a Finnish research institute focused on molecular medicine research (FIMM). In addition, I have questioned how FIMM's research is linked to the broader healthcare visions associated with personalised medicine. In my analysis, I have followed Bruno Latour's vision of sociological research where "the task of defining and ordering the social should be left to the actors themselves, not taken up by the analyst."[358] This aim in mind, I have described and analysed the research at FIMM as it was narrated and performed by the researchers themselves. This chapter aims to connect my research findings with the current feminist discussions about the role of materiality in feminist theory to elaborate how my analysis of systems medicine research could benefit feminist science studies and *vice versa*.

In the previous chapters, I have used the concept of gender as an analytical tool to help to situate FIMM's systems medicine research as a part of larger changes currently happening in molecular medicine research and its embeddedness to societal healthcare planning. In Chapter 2, acknowledging the category of gender in research was shown to be one of the differences between human genomics and systems medicine research at FIMM. In Chapter 3, I further

[358] Latour 2005, 23.

explained why FIMM's systems medicine researchers do not consider gender differences in their daily research. In Chapter 4, I emphasised that this could be seen as a result of FIMM's research being viewed as an "intermediate step" towards personalised medicine. The comparison between personalised medicine and gender medicine helped to further explain why gender is not seen as relevant for the current systems medicine research at FIMM but also how systems medicine could gain from gendered analysis. This way, I have argued for the relevance of studying gender differences in molecular medicine research, showing both its relevance as seen by FIMM's researchers as well as proponents of gender medicine. What I hope to have conveyed by this point is a sense of the usefulness of gender as an analytical concept when examining systems medicine, even if gender at first might appear irrelevant for it.

My analysis, even if produced through gendered lenses, has been primarily an attempt to understand the rationale behind FIMM's research. In this examination, gender has functioned as a concept that has helped me to clarify practices related to systems medicine. While this work has argued for the relevance of gender focus in molecular medicine research, critically questioning the basis for current gender silences has not been central in my description and analysis of systems medicine research at FIMM. Rather, the gender analysis has stemmed from the investigation of human genomics research and personalised medicine initiatives, with the help of gender medicine literature. These examinations, then, have helped me to explain why and how gender focus would benefit also systems medicine research. Following Latour's guidelines, I have not aimed to explain, for example with the help of extensive literature on gender biases in research,[359] why gender still has so little attention in molecular medicine research. What I have done, instead, has been to show what such gender-inclusive research would require from the viewpoint of researchers associated with human genomics, gender

[359] See, for example, Kourany 2010 for an elaborative account of how gender biases are seen to influence medical research. The feminist analysis of scientific research shows how scientific research is embedded in societal, as well as gender, relations.

medicine as well as systems medicine. This focus, I argue, can form a fruitful basis to consider how systems medicine could benefit from feminist engagement when multiple ways to discuss the basis of gender differences would be brought to medical research. What is more, understanding the current limitations of systems medicine research to address gender differences in disease can help feminist scholars in forming more fruitful ways to engage with current biomedical research.

To explain what feminist engagement would entail, I need to explain in what ways engagement with natural sciences can be viewed as a feminist undertaking. In Chapter 1, with the help of Longino's work on feminist virtues, I explained why systems medicine research would be of interest to feminist scholars. Still, I am left with a question of how my analysis of systems medicine can benefit feminist science studies and possible future engagements with the field.

I will answer this question by examining the ways in which feminist scholarship has approached the research field of epigenetics to form novel ways to include biological information in feminist studies. In this literature, epigenetics is seen to benefit both the ways of thinking how materiality can be productively included into feminist theory and the possibilities of using biological information in political argumentation. To examine the relevance of such literature to my analysis, I will investigate the connection between epigenetics and systems medicine. I will show how epigenetics can be viewed as a field that can support feminist engagement also with systems medicine by arguing for the need to address social inequalities in disease emergence. However, I will show how a focus on systems medicine research can introduce additional consideration that can help to form productive ways to guide discussion between social and natural sciences. Firstly, my analysis can help to explain how gender can be a fruitful concept in forming such collaboration. Secondly, I will argue for a need to consider what kind of research is possible with the big data approach. This approach will help to guide

the discussion from the ways in which scientific research can be used in feminist research towards questioning how one could imagine productive collaboration between the fields.

1. Epigenetics in Feminist New Materialism

As explained in Chapter 1, feminist new materialism stresses that feminist theorists should better consider how matter itself plays an active part in knowledge production. This would require a feminist analysis of scientific research that would go beyond constructionist analysis to see scientific meaning production as always material-discursive. The feminist new materialism has been influenced by Karen Barad's feminist approach to quantum physics,[360] which has introduced concepts such as intra-action and agential realism to feminist scholarship, both of which emphasise matter's agency. Barad's demand to see how "'environments' and 'bodies' are intra-actively co-constituted,"[361] has inspired some feminist scholars to engage with epigenetics research, arguing that it presents similar requirements in biological research.[362] In what follows, after defining epigenetics, I will examine why epigenetics is seen as beneficial in forming a link between feminist and biological studies and how this link can inform feminist politics. I will, then, explain what kinds of challenges are faced when forming such feminist engagements with epigenetics.

[360] See Barad 2003 and 2007.
[361] Barad 2007, 170.
[362] See, for example, Davis 2014 and Weasel 2016.

1.1. Defining Epigenetics

To understand the relevance of epigenetics to feminist theories, as well as challenges in forming feminist engagements with epigenetics, it is important to show how the concept of "epigenetics" has different meanings.

Broadly speaking, epigenetics is a research field that aims to understand molecular mechanisms, beyond DNA sequence itself, which are involved in DNA regulation. Current epigenetics research is seen as a novel take on the age-old question of the interaction between nature and nurture in human development.[363] However, the term epigenetics was formed already in the 1940s by Conrad Waddington to express that in order to understand how an individual's genotype turns into their phenotype, it was not enough to focus on particular genes, but rather to ask how an individual's adult characters "arise gradually through a series of causal interactions between the comparatively simple elements of which the egg is initially composed."[364] In Waddington's work, the term "epigenetics" helped to explain the issue of cell differentiation, in other words, understanding how cells develop to form different kinds of tissues, such as skin or bone. As Margaret Lock and Gisli Palsson emphasise, Waddington "argued that genes are responsible only for guiding 'the mechanics of development,' and phenotypes result from interactions among cellular environments and genotypes."[365] While Waddington offered a general sense of the term further research has examined what kinds of cellular interaction are involved in gene expression.

Recent studies, conducted increasingly after the completion of the Human Genome Project, have helped to understand the molecular mechanisms that take part in DNA regulation.[366] Research has exposed the relevance of epigenetic mechanisms, which include

[363] See Keller 2010, Lock & Palsson 2016.
[364] Waggington [1957], cited in Lock & Palsson 2016, 83.
[365] Ibid., 85–86.
[366] Time after the completion of the Human Genome Project (HGP) is often called a time of "postgenomics", as the completion of the HGP underlined the need to understand not just DNA sequence but DNA regulation in cell biology. See Richardson & Stevens 2015 and Rheinberger & Müller-Wille 2017.

"methylation, acetylation, microRNAs, and histone modification, all of which function as molecular cofactors that repress or activate DNA expression."[367] Importantly, studies have connected these molecular mechanisms to environmental factors—meaning "everything from neglectful mothering and child abuse to a high-fat diet and air pollution"[368]—highlighting how environment can influence gene expression. This process is often termed as "phenotypic plasticity" to emphasise the "ability of an organism to create the phenotype most advantageous in response to environmental change."[369]

As Virginia Hughes comments in her news feature "The Sins of the Father," published in the journal *Nature* in 2014, many studies arguing for a link between environmental factors and molecular mechanisms have received somewhat sceptical reception within the scientific community. This is because it is difficult to prove that a direct link exists between environmental stimuli and molecular mechanisms.[370]

Still, its relevance to medical research is increasingly acknowledged. During my fieldwork at FIMM in 2014, I asked Researcher 7, the leader of human genomics at FIMM, about the relevance of epigenetics to their research. He commented that it is relevant but methodologically challenging as, to study DNA methylation (which has been the main focus in epigenetic studies), one needs to have just the right tissue and the right cell under study. After my fieldwork, a new research group focusing on the epigenetics of complex diseases and traits was formed under human genomics at FIMM. This shows that while there are methodological challenges involved in the study of epigenetics, it has growing relevance in molecular medicine research.

[367] Richardson 2017, 31.
[368] Hughes 2014, 23.
[369] Lock & Palsson 2016, 86.
[370] See, for example, Buchen 2010.

However, a newer use of the term "epigenetics", suggesting a possibility that epigenetic changes can transmit across generations, has raised even more doubt.[371] As Keller writes, this use of the term suggests that "not only are changes in various extra- (or epi-) genetic factors affecting phenotype routinely passed on in cell division, but also such changes can often be transmitted through the generations, despite the fact that they do not involve changes in DNA sequence."[372] One research arguing for transgenerational epigenetics has been the Överkarlix case, conducted in a municipality in northeast Sweden. Based on historical records of harvest statistics, food prices and family histories, the researchers have traced connections between paternal grandparents' food consumption and grandchildren's mortality.[373] As Hughes states, the various results did not fully convince many scientists as "[e]pidemiological studies are often messy, and it is impossible to rule out all confounding variables."[374] For many, the idea of transgenerational epigenetics seems implausible as, though it is acknowledged that epigenetic marks, for example DNA methylation, has a role in DNA regulation, they should be removed at the early stages of embryonic development.[375] Though, Hughes writes, animal experiments since "have supported these observations and begun to attribute the transmission of various traits to changes in sperm."[376]

While the mechanisms of epigenetic heritance are still largely unknown, social scientists have underlined the possibilities that such a research approach brings for interdisciplinary collaboration between social and life sciences. As Lock and Palsson state, "[m]olecular genetics and epigenetics will continue to bring scientific facts to light, but the hope must be for increased

[371] Hughes 2014, 23.
[372] Keller 2010, 5.
[373] See, for example, Pembrey at al. 2006 and Bygren et al. 2014.
[374] Hughes 2014, 23.
[375] Ibid., 24.
[376] Ibid., 23. This also explains the title of her piece, "The Sins of the Father", as the studies on possible transgenerational epigenetic effects often focus on studying the influence of fathers as mothers' environment might influence the foetus during pregnancy, thus possibly undermining the research results. This title, still, seems to be at odds with feminist scholarship showing how epigenetic research (though referring mostly to studies not focusing solely on transgenerational epigenetics) is extensively focused on maternal-foetal interactions. See Richardson 2015.

understanding of the value of different styles of reasoning and for communication across disciplines enabling molecular findings to be embedded in lived and narrated experiences."[377] This sentiment is repeated in feminist research.

1.2. Epigenetics in Feminist Research

For feminist new materialist scholars, epigenetics represents an approach that could help feminist theory and politics to better connect with materiality. As Coole and Frost state,

> [f]or new materialists, no adequate political theory can ignore the importance of bodies in situating empirical actors within a material environment of nature, other bodies, and the socioeconomic structures that dictate where and how they find sustenance, satisfy their desired, or obtain the resources necessary for participating in political life.[378]

Epigenetics has been especially appealing for feminists new materialist scholars because it suggests a link between social inequalities and biological development. As Lisa Weasel argues in her article "Embodying Intersectionality" (2016), "new material-discursive practices are being enacted within and through the science of epigenetics, producing not merely different descriptions of the world, but indeed different material configurations with the potential to participate in the active unfolding of political outcomes important to feminists."[379]

Weasel sees that epigenetics is especially beneficial for feminist theories on intersectionality. She writes,

> The recognition that oppression and privileges along intersecting vectors of gender, race, class, sexuality, ability, and other categories are intermeshed and cannot be isolated from one another or understood as simply additive has sometimes been challenging within feminist analytical frames focusing exclusively on social construction.[380]

While intersectionality has been influential for feminist theories of oppression,[381] Weasel notes that many feminist studies fail to account for "the embodiment of intersectional experience."[382]

[377] Lock & Palsson 2016, 151.
[378] Coole & Frost 2010, 19.
[379] Weasel 2016, 107.
[380] Ibid., 104.
[381] See, for example, Crenshaw 1991.
[382] Weasel 2016, 104.

To develop the understanding of intersectionality in feminist theory and to bring it to feminist politics, Weasel turns to epigenetic studies.

To exemplify her point, Weasel mentions a group of studies that tried to understand why U.S population records on birthweight showed a strong correlation with race. When the results could not be explained by differences in socioeconomic status, researchers hypothesised that the difference had a genetic basis. However, further data showed that there existed a variation within recorded race groups, dividing people based on whether they had recently migrated to the U.S. or had been born there. Thus, Weasel ends the example, "[b]irthweight disparities didn't correlate with race; they correlated with a generational history of experiencing embodied, intersectional racialization leading to the formation of race-gender-class disparities in the socio-material temporal and spatial context of the postcolonial United States."[383] This example shows well, how epigenetics, while stemming from biological data, needs to be open for social analysis to explain its findings. Furthermore, such analysis can then be useful in feminist studies to describe how embodied experiences are formed in a certain context and in relation to social interactions framed through concepts such as race that are not only socially experienced but also biologically transformative.

These kinds of studies, Weasel argues, can be used in feminist politics to raise more awareness on how social inequalities are leaving biological marks to people and, thus, demand social change. In a country like the U.S., Weasel states, epigenetics can bring weight to feminist politics as politicians can no longer claim that such inequalities could be resolved merely by individuals' own actions, for example, by moving to another neighbourhood.[384]

However, Samantha Frost remarks that the focus on biology might end up reinforcing the idea of biological sciences as "proper" knowledge upon which to base politics. This might, then, reduce critical stances towards the sciences and, possibly, lead to a situation where "in accepting

[383] Ibid., 115.
[384] Ibid., 117.

a scientific claim about biology one is being tricked into accepting a noxious assumption or entailment that one certainly would not knowingly or voluntarily affirm."[385] To avoid reinforcing such readings of what the role of biology should be in feminist research, Frost suggests that one could see life sciences "not only as a factual resource but also a figural resource."[386] This way, natural sciences could open new ways of thinking about human existence as embedded in both material and social relations, thus supporting responsible living, but would not be used as a basis for feminist identity politics.

Such a stance is understandable, as biological argumentation can gain ground in ways that can reinforce existing oppression. For example, Katherine McKittrick has raised concerns over biocentric conception of the human as these conceptions often reduce black lives into biological definitions, centred around measurements of death and dying: "Within this framework we can apparently fix and repair the racial other by producing knowledge about the racial other that renders them less than human (and so often biologic skin, only and all body). No one moves. This is what is at stake in all of our intellectual pursuits and analyses of difference."[387] Thus, McKittrick recommends thinking of ways to consider black lives through other means, such as literature.[388]

The concern over biology's role in feminist politics represents a central issue when thinking about the meaning of a *feminist* engagement with life sciences. The fear, indicated by Frost, is that concepts stemming from new approaches in life sciences, such as complexity and complicatedness, are left hollow when brought to feminist theory and biological research is referred to only if it echoes the social complexities we are already aware of.[389] This is an issue raised also by feminist scholars whose research has been focused on epigenetics, such as Weasel

[385] Frost 2014, 309.
[386] Ibid., 307.
[387] McKittrick 2016, 16.
[388] Ibid.
[389] Frost 2014, 321.

and Sarah Richardson.[390] In their work, this challenge is approached not by looking for other bases for feminist identity politics but by encouraging a deeper engagement with the epigenetic research to show not only its potentiality but also its possible pitfalls.

1.3. Theory Does Not Equate to Politics: Feminist Engagement with Epigenetics

Many feminist scholars, when talking about epigenetics, highlight that social scientists should not expect that scientific research would automatically be used in ways that would reduce social inequalities.[391] As Sarah Richardson writes, "[w]hile some invoke epigenetics as a grounding for plasticity-affirming feminist theories, analysis of epigenetic approaches as they are deployed within the on-the-ground language, claims, and cognitive and social practice of this particular area of present-day science yields a different imaginative horizon."[392] Through several examples of present-day epigenetic research, Richardson shows that instead of challenging binary gender models or social inequality, epigenetic research can help to reinforce them.

Richardson challenges the idea that epigenetics would necessarily offer a better basis to discuss sex and gender differences. To exemplify this, she mentions studies on mammalian sex differences in the brain. Recent epigenetic studies have shown that the area of the rat brain, which is known to show a notable sex difference, is not hardwired but actually plastic as it constantly reforms. Still, the researchers themselves and the scientific community more broadly have taken this to prove, rather than challenge, the binary division of sex.[393] In her article "Plasticity and Programming: Feminism and the Epigenetic Imaginary" (2017), Richardson explains this to be a result of the fact that epigenetics has a dual role in basic biology as a study of either human development from a foetus to adult or the study of a causal relation between

[390] Weasel 2016, Richardson 2017.
[391] See, Richardson 2017, Weasel 2016, Lock & Palsson 2016, and Blackman 2016.
[392] Richardson 2017, 45.
[393] Ibid., 31–32.

environmental stimuli and gene expression. As Richardson's prior work has shown,[394] this dual approach operates in an older model of sex "in which genes and chromosomes determine initial sexual fate and gonadal hormones such as estrogens and androgens govern sexual differentiation and secondary sexual traits."[395] Thus, even if research shows phenotype plasticity in bodily areas connected to sex difference, this constant alteration does not necessarily challenge the idea of a stable sex difference. Hence, one cannot assume that the epigenetic theory in itself would form a basis for a new social understanding of gender as material-discursive as sex difference is often already presumed in epigenetic research design.[396]

Richardson has also studied the ways in which epigenetic research focusing on environment-gene interaction influences healthcare planning. In her article "Maternal Bodies in the Postgenomic Order: Gender and the Explanatory Landscape of Epigenetics" (2015), she shows how epigenetic research has been centred on maternal-foetus relation as a possible site to study epigenetics and control its outcomes. In these epigenetic studies, the environment has come to indicate "fetal environment" and the "maternal body, in turn, is conceptualized as an adaptive environment for the fetus in which crucial early developmental cues are transmitted to the growing infant."[397]

Becky Mansfield and Julie Guthman have similarly highlighted the role that pregnancy has in epigenetic-based interventions. Moreover, they see these as racialized interventions, with an "eugenic" aim "towards a privileged, idealized, and white norm."[398] Weasel illustrates Mansfield and Guthman's argument with a description of the case of Kim Anderson, a black attorney, who during her pregnancy was, similarly to an educated white woman, aware of particular nutrition that was seen as epigenetically harmful or beneficial. However, in statistics,

[394] See Richardson 2013.
[395] Richardson 2017, 33.
[396] Ibid., 40.
[397] Richardson 2015, 217.
[398] Mansfield & Guthman 2015, 16.

Weasel writes, "the birth outcomes of highly educated black women on par with white women without a high school diploma."[399] When planning preventative healthcare, these kinds of statistics play an important role in racially monitoring and controlling pregnancies.

The focus on foetal environment in epigenetics also underlines that interventions based on epigenetic studies do not need to be focused on social inequalities or environmental problems, such as pollution, but can be directed at the level of an individual. To demonstrate this, Lock and Palsson refer to Mansfield's study on methylmercury levels in fish eaten by Native Americans, and Bruce Johanssen's study on toxic levels in Arctic animals eaten by Inuit women. Both studies highlight that pregnant and lactating women are guided not to eat local fish or meat to avoid causing developmental problems in their children. In other words, the solution to the problem is directed towards individual women who might not even have proper access to cleaner food rather than environmental protection.[400]

Taking these studies into account, feminist theorists cannot use epigenetics as an approach that would uncritically offer a basis for feminist politics. What these critical studies of epigenetics do, however, is to emphasise the need for social scientists, feminists included, to collaborate in research projects aimed at understanding gene-environment interactions. In what follows, I will consider how these feminist accounts on epigenetics also develop my analysis on the relationship between personalised medicine and gender medicine, started in Chapter 4, and, moreover, how my analysis on systems medicine could open new considerations when thinking of feminist engagement with biomedicine.

[399] Weasel 2016, 114.
[400] Lock and Palsson 2016, 134–135.

2. From Epigenetics to Systems Medicine: Framing Feminist Engagement

Similarly to epigenetics, systems medicine is based on a novel approach to biological organisms that aims to address their inherent complexity on the cellular level. Therefore, both epigenetics and systems biology have been brought up in the feminist new materialist literature as potential inspirations for new articulations of biology in feminist scholarship.[401] However, systems medicine research at FIMM, as emphasised in Chapter 3, does not aim to understand biology as such but, instead, uses a systems biology approach in a more practical quest to examine and form patient subgroups based on their molecular profiles. This is done with the help of drug screenings that show variation in drug responses even though patient-derived cells under study all share the same cancer diagnosis. Hence, unlike the examples of epigenetics mentioned in this chapter, the current systems medicine research is focused on investigating the cancer genome rather than gene-environment interactions involved in its functions.

However, as I showed in Chapter 4, systems medicine research at FIMM can be seen as "an intermediate step" towards personalised medicine. This future direction, I argue, also makes systems medicine as a potentially fruitful site for a collaborative feminist engagement as proponents of personalised medicine aim to combine environmental information to individual disease prevention calculations in the future. In this part, I will investigate the rationale for feminist researchers to form active engagement with systems medicine research. I will start by showing how epigenetics is linked to personalised medicine initiatives. Here, I will show that feminist critical accounts on epigenetics, discussed in the previous section, can also help to deepen my analysis of the difference between personalised medicine and gender medicine portrayed in Chapter 4. I will then move on to discuss the possible additional benefits that a focus on systems medicine research could bring to feminist scholarship owing to its aim to

[401] Coole and Frost 2010, 17.

connect basic research and clinical relevance. Finally, I will question why such an approach could gain relevance if the focus shifted from considering values in scientific research to possibilities in research.

2.1. Epigenetics in Personalised Medicine

Keller ends her book *The Mirage of a Space between Nature and Nurture* (2010) asking why the nature/nurture debate persists even though scientific research has shown that such a distinction makes no sense in practice. Simply, she states, the division remains because of politics: "the particular political, economic, and social values we hold dear."[402] The wish to detect whether something is due to nature or nurture, Keller asserts, comes from a wish to know how to control and change a phenomenon.[403] She uses the examples of farm plant cultivation and animal breeding, where epigenetics has been a pressing question for long. A wish to control phenomena represented in epigenetic studies has also been raised in regards to personalised medicine. As Mansfield and Guthman state "as scientists seek epigenetic *marks* they are not only looking to diagnose, but they are simultaneously seeking a *target*, a site of intervention, something in the body to fix."[404] Lock and Palsson argue similarly, mentioning that epigenetics, even though challenging the previous visions of the human body, will not replace current biomedical practices but, instead, "several sub-disciplines, including preventive medicine, psychiatry, and maternal and child health will be deeply affected."[405]

The importance of epigenetics to personalised medicine has also been discussed in medical literature which envisions a possibility in the future to diagnose and address epigenetic modification similarly to genetic ones in personalised medicine.[406] In addition, in an interview

[402] Keller 2010, 83.
[403] Ibid.
[404] Mansfield & Guthman 2015, 13.
[405] Lock & Palsson 2016, 125.
[406] See, for example, Chadwick & O'Connor 2013 and Rasool et al. 2015.

with Wayt Gibbs, Leroy Hood, when asked about the relevance of epigenetics to P4 medicine, answered that in the later phases following their 100P project (discussed in Chapter 4), "the study team will also examine epigenetics: methylation and other modifications to DNA that can reflect environmental exposures."[407] It is clear then that epigenetics is seen as relevant for the future of personalised medicine.

The relevance of epigenetics as seen by the proponents of personalised medicine also supports my argument made in the previous chapter, which highlighted that the foundation of the difference between gender medicine and personalised medicine is less on personalised medicine's focus only on biological parameters but more on its different approach to disease prevention. I emphasised that in the personalised medicine initiatives, the future of healthcare is largely focused on individuals' own efforts in disease prevention whereas the gender medicine initiatives also emphasise societal inequalities as the basis for gender differences in diseases.

Still, feminist approaches to epigenetics help to maintain that different preventative focuses in gender medicine and personalised medicine should not be seen as contradictory but possibly supporting one another.[408] As Lock and Palsson write, preventive actions directed towards societal sources of distress "will not preclude drug development to reverse individual epigenetic changes, although much more knowledge is needed before such drugs could be handed out by clinicians to their patients."[409] This statement demands attention not only to the possibility for a co-existence of different kinds of prevention and treatment plans but also to the fact that more research needs to be conducted to fully understand how epigenetic mechanisms work.

[407] Gibbs 2014, 145.
[408] It is important to remember, however, that in public discussion, personalised medicine is promoted as an alternative option that would provide economic savings for society. Thus, in economic terms, different preventative healthcare strategies are easily contrasted.
[409] Lock & Palsson 2016, 152.

As epigenetic consideration is included into gender medicine initiatives, studying gender differences can help to further the options for personalised medicine as well. Importantly, though, as feminist accounts on epigenetics have shown, prevention plans directed towards social inequalities should never be seen as necessarily resulting from studies that acknowledge gene-environment interaction. Considering how epigenetics can be included in personalised medicine is a good reminder of this. This is also why, I argue, it is important for feminists to be aware of this link between systems medicine and personalised medicine. Seen this way, systems medicine research is also open for possible feminist engagement that can inform productive ways for social scientists to engage with biomedical research.

2.2. Benefits of Addressing Systems Medicine Research in Feminist Research

Most of the feminist engagements with epigenetics originate in the question of whether natural science can help to reformulate the ways to understand gender-sex as material-discursive. This was also my starting point, as discussed in Chapter 1. However, my analysis in prior chapters has shown that a productive feminist engagement with systems medicine would have to have a different foundation altogether. This is because systems medicine research, at least now, does not include biological variation connected to gender in their analysis but, instead, as told by Researcher 1 at the beginning of Chapter 2, aims to "normalise out" such differences from the data.

Still, as I have underlined throughout this work, this does not mean that gender differences would be irrelevant to systems medicine research. On the contrary, the aim of the systems medicine researchers at FIMM to form active collaboration with clinicians and pharmaceutical to develop treatment options keeps the question of gender differences relevant to their studies. These kinds of research approaches might offer even better possibilities for a feminist collaboration than contemporary epigenetics, as they are already devoted to examining the basis

of difference between individuals in a way that can be applied to social healthcare planning. While epigenetics shares this ambition, it is focused largely on basic research where, as shown by Richardson, binary sex division is still forming research design and analysis. In systems medicine research, recorded gender differences in clinical data present a research challenge as, in genetic terms, such a difference rarely makes sense. Forming feminist engagement with systems medicine research might then help feminist researchers to overcome challenges marked in feminist discussions on epigenetics.

In her article, Richardson cautions feminist scholars thinking of applying epigenetic information to their research. She remarks that epigenetics is still contested by many scientists as it is difficult to prove epigenetic causation and reproduce the study results. Furthermore, a lot of epigenetic research is based on animal experimentation, bringing its relevance to humans into question.[410] Naturally, Richardson resolves, this does not mean that epigenetics could not improve into "a resource for feminist studies of the development of gender-sexed bodies"[411] but this involves active feminist engagement "to critically contest the discursive, ontological, empirical, and methodological terms of epigenetic science itself."[412]

I suggest, however, that rather than focusing on life sciences that already discuss gender and sex differences, it might be more productive to consider ways in which feminist scholars could engage with biomedical research such as systems medicine, which does not acknowledge gender differences in daily research but does see their relevance for the development of the field. In a co-operation with systems medicine, feminist scholars would not be tied to questioning, for example, the relevance of human-animal relation in biomedical research, as that is already prevalent in systems medicine research as shown in Chapter 3.

[410] Richardson 2017, 44–45.
[411] Ibid.
[412] Ibid., 48.

Another potential problem that arises from a focus on biological studies that examine sex and gender is that it easily directs the discussion to values in scientific research. As previous sections have shown, epigenetics has been seen as productive only when the scope is limited to certain studies or to the general theory of epigenetics that coincide with previous feminist social analyses. When moving to examine epigenetic research in practice, feminist engagement can turn into a consideration of why scientific research has failed to live up to the expectations of social scientists. While it is important to be critically aware of the ways in which scientific research is socially embedded and a socially relevant site when talking about social inequalities, this kind of emphasis could constrain an active collaboration with the science-in-making. In what follows, I will show why the value-based approach can limit the possibilities of feminist engagement with life sciences.

2.3.Issues in Highlighting Values in Feminist Science Studies

Discussing values in science has been a central focus in feminist science studies. Janet Kourany's book *Philosophy of Science after Feminism* (2010) uses feminist science studies as an example to show that science is not value-free and that some values can have a positive effect on scientific research. Thus, she challenges the persistent view among philosophers of science that analysis of science should focus on its internal reasoning and logic rather than its social embeddedness. Kourany points out that feminist researchers, such as Carolyn Sherif in psychology in the1970s, conducted more accurate research because they highlighted sexist and androcentric biases in research and worked actively to include non-sexist methods into their research.[413]

Kourany's work is important in outlining reasons why philosophers of science should pay more attention to science's relation to society. From a feminist viewpoint, it is important to note

[413] Kourany 2010, 53.

that the focus on values in scientific research helps to bring together different sides of feminist criticism of science: one that focuses on the ontological representation of gender in science and its link to societal norms and the other which highlights the history of scientific neglect towards improving, for example, women's healthcare. While these two criticisms focus on different sides of research—one on its epistemological basis the other on its application—Kourany's work represents them both as the result of sexism in scientific research.[414]

Here, it is important to maintain that, rather than explaining the pitfalls of epigenetics with scientists' sexism, scholars such as Richardson have made great efforts in showing how such dichotomous gender visions are rooted in the history of biological research on sex-difference. Their engagement with epigenetic research, then, helps to form a critical approach to epigenetics that can not only show its downfalls but also offer a framework in which these issues can be efficiently discussed, thus allowing feminist engagement that could support the development of epigenetics. However, similarly to Kourany's framing, the focus is still directed to the operations of the scientific community and the need to socially examine or/and manage them. The problem with this focus on values is that it leads to an illusion that gendered analysis is held back *only* because of the biased social research conditions. In other words, that science could operate in favour of more equalitarian society if only it would gain help in guiding its research practices and strategies towards more egalitarian grounds.

My criticism towards value-based feminist analysis of scientific research stems from Latour's approach to sociology. The challenge of the Latourian approach is how to combine the knowledge of how things work with social and political consideration of how things should be, in his words, "the search for political leverage"[415]. This is where Latour introduces similar concerns as Kourany, as he remarks on the importance of considering how different kinds of

[414] See Kourany 2010. Both of these approaches are present in Kourany's book from the start and no great distinction between them is made.
[415] Latour 2005, 241.

"social stuff" make actions possible. However, he insists that, "the laws of the social world may exist, but occupy a very different position from what the tradition had first thought. (…) They don't cover, nor encompass, nor gather, nor explain; they circulate, they format, they standardize, they coordinate, they have to be explained."[416] This also explain his approach to things that are not yet done, but should be done.

Latour maintains that sociological analysis can be helpful in determining not only what is done but also helping to form a better understanding of what is not done. He calls these undone possibilities "background plasma", which "is not yet formatted, not yet measured, not yet socialized, not yet engaged in metrological chain, and not yet covered, surveyed, mobilized or subjectified."[417] Sociological research, Latour concludes, can help to narrate how current actions take place within social conditions open to other actions as well. Thus, rather than aiming to form a "critical distance" to the studied field, sociological studies should aim for "critical proximity".[418] In other words, not only point out what is not done but to consider the situation in which they are not done. This can then also help political actions aiming to enable other kinds of actions. Based on this, I argue that feminist scholars can benefit both by engaging with studies such as epigenetics, which actively address issues of sex and gender, as well as with systems medicine approaches where gender, at first sight, appears irrelevant. Trying to understand how researchers see the possibilities and relevance of acknowledging gender differences in their work can help to further discuss the ways in which feminist analysis could benefit scientific research. In addition, the discussion could then move forward to consider what such research would require.

To be absolutely clear, the opportunities, as I see them, for a feminist scholar to engage with systems medicine are based on the prior work in gender medicine initiatives. The agenda

[416] Ibid., 246.
[417] Ibid., 244. Metrology refers to (science's) aim to form common measurement scales.
[418] Ibid., 253.

to develop gender research in biomedicine has largely been value-based, addressing gender stereotypes and biases in the medical field and the need to face them to produce better research on gendered differences in diseases.[419] Thus, emphasis on values in scientific research should not be disregarded and continuous political action is needed to maintain the importance of actively addressing gender differences in research. However, with the help of gender medicine, feminist engagement with systems medicine could now be based on questioning what is meant by gender and sex in specific research projects. This would then shift the focus from values in scientific research to possibilities to study gender differences in scientific research. This would require taking into consideration how sex and gender, also intersecting with other categories such as class and race, can have different kinds of meanings depending on the focus of the research and the data used in it. What is more, a larger feminist question arises when considering the broader changes connected to systems approaches in medicine: what would it require to study gender differences in data-centric research? I argue that forming feminist engagement with current molecular medicine research approaches requires an analysis that goes beyond particular research programs to examining how biological data is gathered, organised and accessed.

3. Feminist Engagement with Systems Medicine Research

To form feminist engagement with current systems medicine research requires consideration of the ways in which scientific facts are constructed. In his earlier works, Latour examined the construction of scientific facts,[420] the assumed connection between science and modernity,[421]

[419] Schiebinger 2012, 6.
[420] Latour & Woolgar 1986.
[421] Latour 1993.

and science as social practice[422]. In these works, he has been keen to show how constructionism is an internal part of scientific practice. He highlights that scientific constructionism has been ill-treated in the discussion of social constructionism, which has focused on science's inability to account for "the real". Rather, he emphasises, in science, "facts were facts—meaning exact—*because* they were fabricated—meaning that they emerged out of artificial situations."[423] Thus, what matters in scientific research is not whether facts are constructed but whether they are badly or well-constructed.[424] This emphasis on scientific construction is central when considering how gendered differences could be studied in scientific research.

3.1. How to Talk about Sex and Gender in Systems Medicine Research?

The work established in the field of gender medicine can offer a productive basis to discuss how gender could be applied to systems medicine research. This is because there now exists more openness towards gender approaches in biomedicine and gender consideration can also be emphasised in research funding. For example, Ineke Klinge points out that in 1997 "commitment to the gender mainstreaming of all EU policies was made a fundamental principle of Community Activity in the Treaty of Amsterdam. Since then, mainstreaming gender equality has become a topic in various community policies and activities, in member states, and also in EU science policies."[425] Gender medicine promoters, who actively search for possibilities to inform more scientists about the relevance to acknowledge gender in molecular-level research, also offer practical guidance on how to do this. One such example is the LIBRA project, which began in 2015, that FIMM is also a part of.[426]

[422] Latour 1987 and 1999.
[423] Latour 2005, 90.
[424] Ibid., 91.
[425] Klinge 2007, S60.
[426] For the information of the project, see: <http://www.eu-libra.eu/> [Accessed 25.2.2018]

As mentioned in Chapter 4, I returned to FIMM in May 2017 to interview Researcher 9 and Researcher 16 about the LIBRA project. This was the only interview where I talked with two people at the same time. The element of group interview helped to highlight what challenges researchers see in gender approach as the interviewees also asked for clarification from one another. This interview made it evident that it is still unclear to many researchers in molecular medicine how the gender approach could be relevant for their research.

One of the biggest challenges in applying the gender approach to molecular medicine is definitional: what is meant by "sex" and "gender"? When I asked how the LIBRA project has approached its aim to support "sex and gender dimension in research", Researcher 9 described her participation in a LIBRA workshop, held by Ineke Klinge, which introduced possible ways to consider, for example, male and female differences in animal experimentation. Researcher 9 stressed that for her, "that was the first time I had had such a presentation. So I had not been aware of this." After Researcher 9 mentioned this workshop, Researcher 16, who had not participated in this particular meeting, asked for clarification. This turned into a dialogue that showed well how unclear the concepts "gender" and "sex" can be:

- *Researcher 16*: Did it come up as to why they refer to this as 'gender dimension' in research? Because it is clearly only sex that they are talking about. So, I'm so confused when people talk like 'the gender' of their cells—it makes absolutely no sense.
- *Researcher 9:* My understanding is that sex is the actual biology, so the cell biology. So, you know, chromosomes of your cells. And [when] talked about gender then it's the behaviour and it's the… overall baggage.
- *Researcher 16:* That would make sense for social sciences, to talk about gender dimension in research, but then in these kinds of sciences, I don't see any sense in talking about 'gender dimension' in research. I see a sense in talking about *sex* dimension in research. This woman who came to talk—did she clarify these terms to people? People around here are using them incorrectly all the time.
- *Researcher 9*: I mean, yes. But you have the gender, you know, for the population studies for example, for genetics. Because then you still talk about gender.
- *Researcher 16:* But that's still sex, though.
- *Researcher 9:* It is still the sex, yes. But there might be behavioural differences between the genders that might impact on your…
- *Researcher 16*: That's true, there might be, yes. [Impact on] your gene expression.
- *Researcher 9:* Exactly.

In the interview, this was the first point at which we talked about the sex and gender dimension in research and the above dialogue shows well how the initial reaction to these concepts can be confusing. Gender medicine workshops, here represented by Researcher 9 who had participated in one, can help to show what is meant by these concepts and how they relate. The issue of the definitional murkiness of sex and gender is acknowledged in gender medicine literature, which underlines the need to form a clear understanding of these terms to analyse gender differences in medical research.[427]

However, from a feminist perspective, the ambiguity of the terminology is also the outcome of one of the most important aspects of gender medicine: the requirement that sex and gender should be seen as possibly intertwined in disease aetiology. As John Dupré underlines, in the era of postgenomics, it makes little sense to try to draw a clear distinction between sex and gender as studies increasingly show their linkage and dynamics.[428] Recent studies have suggested that not only are human bodies open to epigenetic influences but individual's cellular sex can contain both "male" and "female" cells. As Claire Ainsworth states in her article "Sex Redefined", published in *Nature* in 2015, "new technologies in DNA sequencing and cell biology are revealing that almost everyone is, to varying degrees, a patchwork of genetically distinct cells, some with a sex that might not match that of the rest of their body."[429] This is hardly surprising to feminist scholars, having read Fausto-Sterling's critical take on the sex binary in biological sciences.[430] What is new, however, are studies suggesting that this cellular sex composition might change during one's lifetime as studies has shown signs of "microchimaerism" where male foetus' cells have crossed to mother's body through placenta

[427] Oertelt-Prigione 2012, 13.
[428] Dupré 2017.
[429] Ainsworth 2015, 288.
[430] Fausto-Sterling 1993.

and *vice versa*.[431] Feminist engagement with systems medicine could, then, help to keep the definition of sex and gender as open as possible in research.

It might well be that in a particular research project, which, as Latour reminds us, is always focused on a particular research question that limits its focus only to certain parameters,[432] research might end up staying in the conventional limits of biological sex. However, what the gender medicine approach suggests is that when planning a research's design, researchers should keep an open mind towards the variety of possible factors influencing gender variation in clinical data. As my interview with professor Eva Gerdts imparted,[433] when addressing the reasons behind gender differences in clinical data, one cannot fully know what kind of data turns out to be relevant when examining disease aetiology. As shown in the dialogue between Researcher 9 and Researcher 16, the gender medicine approach can help to navigate the process of showing why gender difference in molecular medicine research is not only about chromosomal sex difference and, thus, why research design should include gathering various kinds of data.

Moreover, as Gerdts' example of the difference between women from East and West Germany, discussed in Chapter 2, shows, this difference might require an intersectional approach including not only gender analysis but one addressing differences based on class, race, ethnicity, and so forth. Remembering Weasel's argument about epigenetic study discussing racial differences in birthweight (see subsection 1.2), concepts thought as only biological might turn out to be socially induced. Hence, a plethora of data could be needed to address gendered or other variations in clinical data. This produces a challenge for data standardisation.

[431] Ainsworth 2015, 290.
[432] Latour 2005, 240.
[433] As mentioned in Chapter 2, Professor Gerdts from the University of Bergen has studied gender differences in cardiovascular diseases.

3.2. Gender and Data Standardisation in Biomedicine

Standardisation in medical research and clinical studies has been a central issue in feminist science studies because female bodies have long been considered more challenging to standardise owing to menstruation and possible pregnancy. Historically, this has led to the exclusion of women from clinical studies.[434] Thus, when thinking of possible feminist engagement with current biomedical research, it is important to consider the role of standardisation in research.

As Latour states, rather than seeing scientific research as something that aims to cover all possible explanatory options within one research, studies are assessed in accordance with their ability to limit their focus to "only one standardized version of assemblages."[435] For example, when studying different outcomes of a drug treatment between male and female patients, as described by Researcher 2 in Chapter 2, the approach can be limited to studying hormonal differences as prior research indicates that hormones can affect drug responses.[436] The evaluation of the study, then, is not based on its abilities to address all the possible reasons behind drug effects but on the accuracy with which the research can consider hormonal-based differences between patients' drug response. Because previous studies indicate that hormonal differences are a likely cause of differences in patient's drug sensitivity, it makes sense to focus on hormonal differences when examining gendered differences. Furthermore, results gained from studies on hormonal differences between genders could be reproduced, validated and further studied by other scientists, thus establishing it as a well-constructed scientific research. In this example standardisation is based on already established research hypotheses that link gender to biological sex differences that can be measured from patients' samples. Moreover, as

[434] Schiebinger 2003.
[435] Ibid., 240.
[436] See Spoletini et al. 2012.

the difference is seen to be a hormonal one, the expectation is that further knowledge of these differences could be gained from animal models.

However, as more information of possible gene-environment interactions is emerging, the possibilities of addressing sex-gender relations in research design come pressing. Importantly, this would mean producing standardised data also of environmental factors such as nutrition and lifestyle. In ensuring that such data would be collected in a standardised manner—considering, for example, possible national differences when translating terms in international comparative studies—and analysed in relation to the study context, biomedical research could benefit from collaboration with social scientists. At the end of our interview, when considering the possibilities of including the gender aspect in molecular medicine research in the future, Researcher 16 acclaims the possibility of such a collaboration: "I think it's multidisciplinary kind of research that we should be moving towards and not just [by] looking at one and the other but how can we bring behavioral [scientists]—sociologists, psychologists—into working with our cell biologists."

Gender medicine literature suggests the same. As Sabine Oertelt-Prigione writes, "the analysis of the comprehensive meaning of gender differences as modifying factors of health and disease might need the inclusion of methods from disciplines other than medicine and biology, such as psychology, sociology, anthropology, and others."[437] In forming feminist engagement with systems medicine research, it is essential to note that the basis for the relevance of such an engagement is already formulated within the scientific community, thus reducing the risk of seeing this collaboration as a necessary confrontational meeting between "two cultures" unable to understand one another.[438]

[437] Oertelt-Prigione 2012, 13.

[438] "Two cultures" refers to a famous lecture-based text by Charles Snow from 1959 where he describes the striking division between natural sciences and humanities scholars in Cambridge to the extent that they could not understand the basic principles of each other's disciplines. This term is still sometimes used to describe differences between natural and social sciences. See, for example, Lock & Palsson 2016, 6–7.

This reading of data standardisation portrays it as a possible connecting aspect between researchers from different disciplines. However, in this framing the data standardisation is based on the assumed correlation between certain measurable biological and environmental differences in a set research strategy. However, as Sabina Leonelli stresses in her article "What Counts as Scientific Data? A Relational Framework" (2015), it is important to examine not only the ways in which data is produced according to the standards that enable a certain research project but how this data is then used in other studies.[439] This question is increasingly prevalent in data-centric approaches in biology.

3.3. Approaching Gender Differences in Data-Centric Biology

When forming feminist engagement with systems medicine, it is important to remember that a defining aspect of the research is its link to big data. Leonelli's work helps to consider how the big data approach has altered the production and use of data in biological research. Based on her studies on biological databases, she highlights that while she applauds Latour's work in pointing out the relationship between scientific standards and data mobility, she is critical towards the assumption of "stability" in this account. She points out that "when travelling from their original context of production to a database, and from there to a new context of inquiry, biological data are anything but stable objects."[440] She continues noting that "scientists engage in data generation in full awareness that the outputs of that activity need to travel beyond the boundaries of their own investigation."[441] At FIMM, this logic can be seen in the emphasis on the importance of establishing and maintaining biobanks that aim to produce data beyond the current needs of their own research, which would be also accessible for international medical research.

[439] Leonelli 2015, 816.
[440] Ibid.
[441] Ibid.

When considering the possibility to use collected data in other research strategies, it is essential to grasp how Leonelli defines data-centrism in scientific research. In her book *Data-Centric Biology* (2016), Leonelli further emphasises how this view on data mobility is required to understand the current data-centric approach in biological sciences. The data-centric approach, she highlights, is challenging the assumption of scientific research being theory-centric as computational technologies enable researchers to generate increasing amounts of data, which is especially notable in the field of molecular biology.[442] She writes,

> We are not witnessing the birth of a data-driven method but rather the rise of a data-centric approach to science, within which efforts to mobilize, integrate, and visualize data are valued as contributions to discovery in their own right and not as a mere by-product of efforts to create and test scientific theories.[443]

Making a distinction between the data-driven method and the data-centric approach further emphasises Leonelli's dedication to show the extent to which data cannot be understood as representing only the research context in which it was produced.

Following this logic, it is important to see how FIMM's research aims are linked to their dedication to collect patient data in biobanks as well as grasp the extent to which data collected in multiple other places is integrated into their research. Thus, Leonelli notes, "one consequence of this view is to abandon the idea that it is possible to pick one 'best' interpretation of data irrespectively of context, both when trying to create techniques and infrastructures to make data travel and when assessing the worth and quality of specific data-centric initiatives."[444] Data, in other words, can gain very different meanings and roles depending on what kind of other data they are combined with and what kinds of questions the study aims to answer. Thus, Leonelli argues that data is not a representational entity in itself but gains the role of 'data' only in situations where researchers see it beneficial for their investigations.[445]

[442] Leonelli 2016, 3.
[443] Ibid., 1–2.
[444] Ibid., 190.
[445] Leonelli 2015, 817–818.

This is important when examining data's relation to studying gendered differences, as Leonelli notes that rather than focusing on the level of manipulation of the studied data it would be more fruitful to "focus instead on the relation between researchers' perception of what counts as data and the stages and context of investigation in which such perceptions emerge."[446] Following this reasoning, it makes little sense to question, for example, whether hormonal differences can explain all gendered differences in diseases. Rather, hormonal differences should be seen as possibly beneficial focus points in studying gendered differences in drug sensitivity in patients while simultaneously asking whether the collected patient data can also benefit other kinds of research focused on examining gendered differences.

Biomedical research is now opening up for the possibility to include environmental data to research. However, what would it mean to approach environmental data in a data-centric manner? In other words, to collect data on people's nutrition, exercise routines, hospital visits, medications, stress, and depression—to name a few possible environmental aspects that could influence disease emergence—not for a specific study but for a potential future use. This is a question that requires a step away from the value-based analysis focused on values of scientific communities to question the possibilities of conducting gender analysis in research. This is because this question is not only asking how science can integrate such data but what kind of information is accessible and *movable*. Therefore, if we want to take seriously the possibilities of forming gender analysis in systems medicine, we need to also ask how such data could be gathered, organised, and accessed.

As I wrote in Chapter 4, with the examples of biobanks, this is a question that is not only a practical challenge of institutional organisation but also raises ethical, political and legal debates. Hence, feminist analysis of systems medicine research, and molecular biology more broadly, should go beyond considering whether gender is included into molecular research to

[446] Ibid., 817.

actively engage in discussions concerning big data approaches in biomedical research. Gender analysis can help to grasp what is at stake in this kind of wish to gather environmental data and how lifestyle information can help to change the questions that the researchers can answer. But in doing so, it is important that the discussion, feminist analysis included, consider this not only as a scientific issue but a social, political, legal and ethical one. Possible productive questions include to what extent do national biobanks improve national health; are samples and clinical data used in projects that would help to address environmental factors in disease emergence? Actively operating in this new relationship between science and society, feminist engagement with systems medicine can maintain its social relevance while effectively supporting research approaches that work towards better accounting for individual variation in diseases.

In this chapter, I have examined how feminist scholars could form productive engagement with systems medicine. A broader aim of feminist engagement, as described with the help of examples of feminist approaches to epigenetics, is to strive towards an equal society. Thus, the success of a feminist approach cannot be measured only by asking whether gender is included into research analysis but whether research can produce reflective knowledge that could be useful in tackling social inequalities. Feminist studies on epigenetics have stressed this point. My analysis on systems medicine has shown how awareness of environmental influences on individuals' biology can be used in healthcare prevention that focuses on individuals' rather than social problems. However, these two preventative strategies should not be considered as necessarily contradictory. Rather, personalised medicine could benefit the development of understanding epigenetics and other possible reasons behind gender differences in diseases.

As systems medicine aims to bridge the gap between basic research and clinical interventions, gender can be a useful term to guide collaborative projects between social and medical scientists. Moreover, the definitional ambiguity of gender and sex in the medical field

could offer a fruitful basis for interdisciplinary collaboration. However, feminist engagement with systems medicine requires an active analysis on the ways in which the data-centric approach in medical research is currently altering the relationship between society and scientific research. To study gender differences in a big data framework requires also active social engagement that questions how individuals' data is gathered, organised and accessed. Seen this way, feminist engagement with systems medicine needs to go beyond the practices of particular research institutes to ask how it would be meaningful in feminist politics to discuss the relation between scientific research, clinical data and organisation of healthcare.

Conclusion

In this dissertation, I have used the concept of gender to examine possibilities for a feminist engagement with systems medicine. My analysis has been founded on the systems medicine research conducted at a molecular medicine research institute (FIMM) in Finland. I have aimed to follow Bruno Latour's sociological methodology that gives the central stage for research subjects to define their work. This is mind, I have presented FIMM's systems medicine research as it was described and practiced by FIMM's researchers. However, the concept of gender has helped me to consider the difference between systems medicine and human genomics research at FIMM and the possible future challenges to develop systems medicine research towards personalised healthcare practices. The concept of gender has enabled such an approach because of the increasing emphasis of the need to address statistical gender differences in diseases that has led to the formation of gender medicine within medical community. I have used gender medicine literature in framing my analysis because, rather than giving a set approach to studying gender differences, gender medicine literature emphasises the challenges in addressing gender differences, seen as both biological and social. With the help of gender medicine literature and through the analysis of the contemporary molecular medicine research, this work has aimed to show the value of feminist engagement to understanding the extent of changes happening now in biomedical research. Moreover, this work has aimed to consider the basis and the possible challenges for future feminist engagement with systems medicine.

This work contributes to existing literature on feminist science studies and new materialism. I started the dissertation with a shocked utterance by a repairman, said after a technician had explained that the metal frame she was holding up contained cancer cell samples. I have often returned to this event and to the consideration of the difference between illness and disease that followed. In the introduction, I presented Annemarie Mol's argument that

differentiating experienced "illness" from a studied "disease" often leaves the definition of the disease itself without scrutiny. The memory of the repairman's shock and my own initial irritated reaction to his words has been a reminder of the importance to keep both the structure of the scientific research and its social relevance in mind, and to consider how the settings in which a disease such as cancer is considered shapes the meaning we give to it.

It has been a difficult task to challenge the distinction between illness and disease, as my work has focused on the molecular-level research done at FIMM, and I have tried my best to write a focused dissertation rather than a complex mind map of all the relevant issues. My aid in tackling this has come from feminist science studies, especially from Helen Longino's work on feminist virtues. Longino's list of feminist virtues, as described in Chapter 1, has forced me to question the ontological assumptions upon which the research is based, its methodological possibilities, and its social embeddedness. This list has helped me to consider what it means to form a feminist engagement with systems medicine research. I have drawn extensive inspiration also from feminist scholars working in the field of feminist new materialism, such as Sarah Richardson, Samantha Frost, and Lisa Weasel, in thinking how new approaches in biological research introduce innovative possibilities to consider the role of materiality in feminist scholarship. Still, Longino's work, and feminist science studies more broadly, has on several occasions reminded me of the potential usefulness of gender-based analysis. In my analysis, I have shown how the concept of gender can help to see the possibilities and limitations of current molecular medicine research. Moreover, I have shown its use in considering the future possibilities of personalised medicine in a way that helps to see value of feminist research in addressing the broader social implications of the systems medicine approach.

Gender has been a useful analytical tool in my research for two reasons. Firstly, as a commonly used statistical concept in clinical research, it has made it possible to steer interviews outside of researcher's own studies, to questions possible other routes that the research can, or

cannot, take. As such, it has helped me to visualise the aims and limits of FIMM's research. That way, the concept of gender has helped me to map out the whole dissertation. Secondly, it is an evasive concept that lacks one definite relation to molecular research. It is a concept that some see synonymous with "sex", others are lost with its meaning, others feel the need to ask a clarifying question ("you mean sex difference, right?"), others connect it with lifestyle and social sciences. The uncertainty linked to the term itself made it sometimes difficult to ask questions but other times it made it possible to ask follow-up questions that would help to contextualise particular research projects. It was this vagueness in term that enabled me to come to the, what I consider, one of the most fruitful arguments in this dissertation when considering feminist engagement with systems medicine research: scientific research on gender difference should not be only judged according to assumed value biases in scientific work but more attention should be paid to considering what kinds of questions scientists can ask with the information they have. This addition to discussion is needed because it helps to emphasise the larger changes happening in biomedical research in relation to big data, especially when considering the organisation of preventative actions in national healthcare.

As medical researchers are increasingly aware of the need to consider gene-environment interactions in complex diseases—and legal, political and ethical plans are being made to enable this kind of research with the help of biobanks—the possibilities and hopes for future research are taking place. Gender, as a concept, can bring forth both the need for such research and its challenges. Due to its evasiveness, it can remind of the difficulties in determining the reason(s) behind recorded differences between male and female patients. More information gathered, for example, on lifestyle differences could then help to study different possible scenarios. As it is central to gather standardised data, the question of the possible gender differences can then not be an afterthought in research but, as proponents of gender medicine underscore, need to be considered from the start. The evasiveness of the concept of gender is, in addition, a reminder

of the fact that big data in itself does not offer better understanding of diseases. Even if more versatile data would be available for mathematical modelling, this data still needs to be integrated in a meaningful way. Still, what can change with the big data approach are the possible questions that can be asked.

When I started my fieldwork, it seemed that gender was nowhere to be found in FIMM's systems medicine research as the work was focused on a molecular level. Rather than seeing this silence as an outcome of biased research practices, I could understand how the aims of the work at that moment were tied to questions that needed to be answered before potential gender analysis. This vision was reinforced by the discussions I had with researchers, who envisioned gender as an interesting approach in their future research. However, further examination into the connections between molecular research and individualised medicine raised questions of the need to study gender differences in some aspects of the research. Comparison to human genomics research, as discussed in Chapter 2, gave grounds for more detailed considerations of what was, and what was not, done when considering gendered differences in disease aetiology and treatment planning.

Feminist science studies has also kept reminding me of the need to not focus solely on epistemological questions in knowledge production but also consider how research is affecting medical practices. During my fieldwork, it became obvious that hopes for personalised medicine have shaped the discourses and practices around systems medicine research at FIMM. Many researchers highlighted the importance in working together with clinicians, and applauded the possibilities to help current patients. Research projects were funded with applications sent in for personalised healthcare calls and seminars were organised to bridge the gap between basic researchers and medical professionals. Some rarer moments also revealed the doubts regarding the future possibilities: the high-cost of personalised medicine or the limitations in considering the overall wellbeing of people. Those moments, connected to my

critical readings on social limitations in personalised medicine and its possible drawbacks, reminded me of the lived reality of diseases and reconnected me to that moment when I was shocked to hear repairman's exclamation in the storage room. The need to consider the context of research is essential for feminist researchers as it helps to consider the broader implications of new research methodologies relying on big data.

The value of addressing the basis of gender differences in diseases is already underlined in gender medicine literature. The field of gender medicine is tied to current situation in medical research and has clearly shown the necessity of raising awareness of gender differences in diseases and to emphasise that personalised medicine does not fully address the role of gender as a risk factor. However, I would resist a juxtaposition between personalised medicine and gender medicine. Such contrast might create too limited a view of the goals of personalised medicine by focusing only on its current abilities. As I pointed out in Chapter 4, personalised medicine literature emphasises the wish to include lifestyle information and, thus, its current emphasis on biological information should not be seen as its defining element. The avoidance of such a juxtaposition could introduce ways to include gender perspective better in current research, as an important part in developing personalised medicine. As my fieldwork showed, questions about gender are not currently considered in systems medicine research and their role is largely seen as statistical, making it difficult to see the value of gender approach in the framework of systems biology that aims to understand the complexity of biological mechanisms. Much work is, then, needed to enable such collaboration. However, as systems medicine moves towards clinical relevance in a broader scale, more gender differences can occur in some diseases and their treatment. Then, a more detailed questioning of the basis of such differences, including environmental information, containing lifestyle data, can become necessary. In this way, I would see gender approach to support rather than differ from the aims of future systems medicine.

An addition that a feminist approach can make to this discussion is to investigate larger social changes envisioned with personalised medicine. It is important to see the value of gender medicine not only as an additional aspect that should be combined with the personalised approach but as a pathway to address broader social structures possibly influencing gendered differences in diseases. As I have argued, a feminist approach would both emphasise the value of gender approach to produce better medical research, tied to research questions of a particular disease, and also function as a social question of whether preventive actions can also be directed towards social inequalities. As I wrote in Chapter 5, feminist studies on epigenetics have emphasised that research showing how biological mechanisms are linked to social inequalities can be used in political argumentation against social inequalities. Similarly, feminist engagement with systems medicine should go beyond particular research settings to stress that a personalised take on medical healthcare planning should also support individual wellbeing in a community. As I have emphasised in this work, social and personal preventive strategies are all but contradictory. They support one another and should be regarded as such. However, the economic realities, especially the discussion of the need to show how personalised approach would in the long run produce beneficial economic effect, might push these two strategies as exclusive. This is why feminist engagement is needed. There is still great value in one of the central slogans of feminist political movements—"personal is political"—which emphasises the need to consider how individuals' problems can be linked to social inequalities. Thus seen, health-related issues should not only be seen through individualised screening practices.

From a perspective of natural scientists, it can be sometimes difficult to see what kind of relevance social scientists can have for medical research. While I was warmly welcomed at FIMM, and some researchers emphasised the value of collaboration between social scientists and medical researchers, I also got used to realising that the reason for my stay at FIMM had remained unclear to many. Some, for example, started the interview describing how being male

or female can affect the work life, thinking that I, as a gender studies scholar, had come to study gender relations at a scientific workplace. Some raised their doubts by jokingly asking whether I had come to spy their research. While all my interviewees readily described their own research in our interviews, it was clear that my disciplinary background made my inquiries odd as I was interested in learning more about research that did not discuss gender explicitly. Based on this experience, I understand why C. P. Snow's view on two cultures, presented in 1959, is still used to describe the gap between natural sciences and humanities. My work has aimed to show how feminist approach to systems medicine can help to introduce novel approaches and questions that can be of interest also for natural scientists.

As I showed in Chapter 3, while most of the FIMM's researchers know the studied patients only through the sample codes, the increasing requirement for clinical relevance shapes their work. For instance, cancer 3D cell models are developed to resemble human tumours, made increasingly challenging with the aim to try to mimic patients' molecular profile. The wish to address individual differences in treatment is linked to the larger aims connected to personalised medicine that ultimately aim to direct the healthcare focus on disease prevention. The development of preventative plans could open new possibilities for an active interdisciplinary collaboration between social scientists and medical researchers, even at the level of medical research itself.

It is important to see the possible interdisciplinary collaboration as multifaceted. The value that a gender scholar can bring to this field is the ability to stress the importance of studying gender differences in medical research while seeing how the category of gender is vague. This approach is a great advantage when discussing the relevance of gender for molecular-level research as it allows feminist scholars to maintain the importance of a gendered approach without getting caught up in a strict definition of the term which might not be relevant for every research. This approach underlines the value of active collaboration between two

fields rather than seeing gender as a definite concept that could be similarly applied to every research. Furthermore, a gender approach can help to situate molecular medicine research in the broader changes happening now in medical big data research. My work has aimed to offer such "critical proximity" by considering the differences between personalised medicine and gender medicine beyond their current practices and differences. This analysis has hopefully shown that, while it is worthwhile to consider ways in which social scientists could engage with actual practices of present-day systems medicine research, it is also central to contextualise such practices according to long-term plans of systems medicine. The value that social scientists can bring to these discussions should be underlined, considering the magnitude of changes that are envisioned to happen both in the organisation of medical research and healthcare practices themselves.

Gender has been an apt tool to raise these issues as its relevance lies not only in the statistical question marks in medical research but in the organisation of preventive healthcare practices. By grasping both the research and political relevance of big data approaches, feminist scholars could help to navigate the difficulties in imagining the changes now taking place. It is positive to see how new approaches in life sciences have raised interest in feminist scholarship, especially in relation to epigenetics. Even more inspiring is to see more and more feminist scholars engaging with life sciences, considering both their inspiring newness as well as their link to established gendered medical practices. Studies on epigenetics and pregnancy, as described in Chapter 5, are good examples of the ways in which feminist scholarship can help to explain the meaning and possible outcomes of the changes happening now in life sciences. As the medical discussion is exceedingly emphasising the need for individualisation, such accounts are essential in supporting meaningful public discussion in politics and ethics of life sciences.

My analysis of systems medicine research has introduced additional issue that should be considered more in feminist science studies: the role of big data in research. This is a central question for feminist scholars when thinking of the changes happening now in medical research. If one wishes to see more comprehensive studies on the reasons behind individual differences in diseases, one needs to also ask how data to enable this kind of research is collected, stored and accessed. As big data approaches become more mainstream in medical research, we need to start asking to what purposes data is collected and how it can be used.

However, due to the newness of the field, it is difficult to fully explicate the ways in which gender differences might be produced in big data approaches. My research has been based on fieldwork done at FIMM starting at 2014, only six years after the start of its operation. Hence, the research practices that I analyse were all considered as part of small scale "pilot projects", aiming to establish new research methodologies bridging basic research and clinical care. As the research practices were still taking their shape at FIMM, it is easy to understand why many researchers saw gendered analysis as a potentially fruitful future aspect of their research but, simultaneously, were hesitant in considering what gender would mean in such research. Thus, this dissertation has paid close attention in showing the benefits in addressing gendered differences in systems medicine research, both for natural scientists and social scientists alike. As the systems medicine research is gaining ground in biomedicine, future research would gain from a more rigorous analysis, following feminist new materialist scholarship, on the ways in which systems medicine researchers produce the idea of biological complexity while maintaining a pragmatic clinical focus. This question is closely linked with the need to address gendered differences in systems medicine research, argued for in this dissertation, as including gendered analysis in research would require balancing between social categorisation of types of bodies and their individual, material, bodily differences and, importantly, to questioning whether such a distinction makes sense in the first place.

What is more, these should not be seen as abstract questions that can be fully addressed in a general level. My analysis in this dissertation has been tied to the context of western medical research and my fieldwork took place in Finland, which is currently developing a National Genomics program, aiming to make Finland as one of the leading countries in genomic research. Part of this development is the Finnish biobank law, aiming to centralise the organisation and access to biological samples and data. In these discussion, developing molecular medicine is seen beneficial both to population health and national economics. As shown in Chapter 4, personalised medicine is tightly linked to pharmaceutical investments through the development of precision drugs. Institutes such as FIMM gain relevance in pharmaceutical collaborations through their clinical collaborations and access to biobank materials. In addition, I have showed, especially in Chapter 3, how FIMM's research requires large infrastructural and technological investments in order to operate. Thus, one should understand the national investments and aims that were behind FIMM's original launch in 2006. Hence, in future research, it would be very interesting to examine how questions about population health are linked to the discussion of biobanks and molecular medicine research in a national level. To what extent are the biobank and research initiatives made sensible through their benefits to public health? To more clearly understand the particularities in the Finnish context, it would be also beneficial to do a comparative global research. This could offer a fruitful basis for further gender analysis by asking how collected biological and clinical data enables the study of gender differences in diseases and to what extent it is possible to do this in a global scale.

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