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A Critical Analysis

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Doctoral thesis

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Thesis for the Degree of
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NORSK SAMMENFATNING

Denne avhandlingen er en kritisk, historisk-filosofisk analyse av et materiale som beskriver *systemmedisin* som et foreslått, teoretisk rammeverk for fremtidens allmennmedisin. Systemmedisin er systembiologi anvendt innen medisinen. Systembiologi er det biologiske studiet av levende systemer, et rundt 15 år gammelt felt innen biologi som har som mål å koble genomet (DNA) til den menneskelige fenotypen (hele organismen i helse og sykdom). Feltets metodologiske hovedfokus er matematisk modellering og analyse av biologiske systemer ved hjelp av store biologiske data (”big data”) og computer-verktøy.

Allmennmedisin er et generalist-fag med behov for å motvirke fragmentering og å utvikle et rammeverk for å begrepsfeste og håndtere hver enkelt pasient som *en hel person*. Vi er samtidig i dag vitne til en sterk, internasjonal trend i retning av å utvikle *en persontilpasset medisin*. Dette begrepet har dype medisinske røtter og har de siste hundre årene først og fremst vært knyttet til medisinsk praksis som tar hensyn til den enkeltes kontekst, erfaringer, tanker, følelser og mål. De siste to tiårene har dette begrepet imidlertid gjennomgått en omdefineringsprosess som startet med kartleggingen av det humane genomet på 1990-tallet. Systemmedisinen kan ses som en videreføring av dette biomedisinske prosjektets visjon om å «skreddersy» medisinsk behandling og forebygging . Som klinisk rammeverk promoteres den ofte som ”P4-medisin”: Prediktiv, preventiv, persontilpasset og ”participatory” (”deltagende eller ”samhandlende”). Systemmedisinens overordnete kliniske løfte er et rammeverk der individuell prediksjon og forebygging av sykdom, basert på modellering og analyse av person-spesifikke helsedata og hver enkelt borgers aktive selv-monitorering, skal revolusjonere allmennmedisinens nytteverdi.

Det nye og sentrale med systemmedisinen er ikke idéen om persontilpasning, men at revolusjonen skal skje innenfor en ramme som presenteres som *holistisk*. Menneskets kompleksitet og medisinens fragmentering skal takles fullt ut. Dette løftet kan se ut til passe som hånd i hanske med allmennmedisinens teoretiske behov. Nettopp derfor er en kritisk analyse viktig.

Systemmedisinen eksisterer i dag primært ikke som noe etablert rammeverk, men som en *visjon* for fremtiden. Rasjonalet for dette arbeidet er at slike biomedisinske visjoner er viktige fordi de genererer handlinger og prioriteringer *i dag*. Mitt mål er derfor å teste systemmedisins hovedløfter om en holistisk tilnærming som skal lede til en revolusjon i klinisk nytte gjennom preventiv medisin i lys av allmennmedisinens store utfordringer.

Et hovedfunn i avhandlingen er at systemmedisinens teoretikere og visjonærer redefinerer selve begrepet holisme, et begrep som tidligere har vært forbundet med humanistisk medisin. Jeg kaller resultatet "teknovitenskapelig holisme". Jeg argumenterer først for at denne holismen inneholder elementer som i vesentlig grad kan fremme forståelse av hele personer i medisin. Spesielt vektlegger jeg i den sammenheng systembiolog Denis Noble´s begreper biologisk relativitet og "nedadvendt kausalitet" (downward causation). Deretter argumenterer jeg for at teknovitenskapelig holisme ikke kan forventes å lede til en humanistisk helhetstenkning som tar høyde for alle elementer ved menneskets kompleksitet. Rammeverket kan i teorien ikke bli mer holistisk enn feltets matematiske og computer-baserte modeller og algoritmer, og biologisk teori mangler i dag adekvate modeller for fenomener som liv, verdier og mening.

Mitt hovedargumentet i avhandlingen er at systemmedisinens løfte om en revolusjon i klinisk nytte basert på persontilpasset, preventiv medisin er upålitelig. Systemmedisinens holisme innebærer det som kan kalles en *holistisk medikalisering*: hver enkelt persons livsprosess – uansett hvor kompleks – blir definert som kontrollerbar og underlagt en form for kontroll som er *alt-omfattende*. Systemmedisinens kontroll er rettet mot alle nivåer, fra DNA til sosiale faktorer, mot hele livsløpet og mot hele spekteret av tilstander fra sykdom, via risiko til optimalisering av friske. I tillegg kan det "samhandlende" (participatory) aspektet ved visjonen ses som en form for *selv-medikalisering*. Denne holistiske medikaliseringen er forbundet med risiko for bivirkninger (skade) og kostnader som systemmedisinens visjonærer så langt ikke har adressert samvittighetsfullt. Med dette som bakgrunn argumenteres det for at det er et motsetningsforhold mellom systemmedisinens hovedløfter og menneskelivets kompleksitet, uforutsigbarhet, og ukontrollerbarhet.

ABSTRACT

Background

Primary care medicine (general practice) is, as a generalist discipline, faced with the key challenge of counteracting fragmentation and developing a framework for conceptualizing and approaching patients *as whole persons*. At the same time, we are today witnessing a strong international focus on the development of *personalized medicine* that is tailored according to factors defining each person uniquely. This concept is as old as medicine itself. However, while personalized medicine has historically been a humanistic concept, it is today rearticulated in a technological and scientific context, starting with the sequencing of the human genome around the year 2000. Systems biology is a 15 year-old biological movement at the vanguard of this development, with the prime aim of making sense of the genome and its relationship to the whole organism (phenotype) through computational and mathematical modeling. Systems medicine, the focus of this thesis, is the emerging medical application of systems biology to medicine. What is new about systems medicine – and critical to the current argument – is that it promises to further the concept of personalized medicine in a way that is no longer reductionist or gene-centric, but *holistic* or *integrationist*. It promises to do justice to the full complexity of human health and disease and to counteract fragmentation in medicine. Thus, it intriguingly promises a new framework for medicine that theoretically seems to fit perfectly with the needs of primary care medicine. Through its new holistic personalization, and a strong focus on patient participation, systems medicine is also envisioned as enabling a new era of predictive and preventive medicine. This concept is often called *P4 medicine* (predictive, preventive, personalized, participatory). The overarching practical promise of "P4" systems medicine is a revolutionary paradigm shift leading to a better overall utility of medicine, a better balance of benefits and harms. At the same time, systems medicine is envisioned as based in primary care, and its promise of a revolution therefore depends on its ability to meet the challenges of general practice. Crucially, systems medicine emerges at a time when biomedicine, particularly individual-centric preventive medicine, has become a very expansive endeavor that is coming under increasing criticisms for fragmentation and overmedicalization, leading to questionable utility and sustainability.

Although systems medicine is in the process of changing the medical landscape, it exists mostly as a vision. This analysis is based on the premise that development of biomedical

visions and promises about the future are important in guiding medical actions and therefore in itself forms an important part of biomedical practice.

Aim

The aim of this study is to test systems medicine as a *proposed*, theoretical framework – its philosophy, visions and promises – against the challenges facing primary care medicine. In particular, it tests the promise of a *holistic* personalized medicine that will lead to a revolution in the clinical utility of primary care medicine. This task is operationalized through more focused research questions. The underlying objective is to contribute to critical reflection, theory development and quaternary prevention (i.e. prevention of medically induced waste and harm) in general practice.

Material, methods and theory

This thesis is methodologically situated in the medical humanities, drawing on philosophy of science in practice and history. The aim is pursued through a critical, historical-philosophical analysis of a primary material consisting of publications proposing systems medicine as a future framework for primary care, as well as some early empirical results. It draws on a secondary material that describes challenges facing primary care, key philosophical topics and analytical perspectives, as well as research on systems biology and medicine from various fields.

Results

A key finding is that the very concept of holism, which has previously been associated with a humanistic form of personalized medicine, is redefined in systems medicine and given a novel technoscientific meaning. The result is called a technoscientific holism. It is shown how this new holism brings substantial philosophical innovations for understanding and approaching whole persons (papers I and II). In particular, it is argued that the philosophy of systems biologist Denis Noble and the concepts of biological relativity and downward causation, might represent a significant contribution to conceptualizing the relationship between "bio", "psycho" and "socio" in the biopsychosocial model (paper I). However, despite these constructive theoretical developments, it is argued that systems medicine cannot be expected to fully counteract fragmentation in medicine and become a genuinely holistic, personalized or humanistic medicine. Although it is promised as holistic, it can in practice be

no more holistic than its computational and mathematical models. It also still involves a strong molecular focus and continued reductionism. It faces fundamental problems in conceptually and methodologically accounting for living wholes, in integrating all components of the complexity of human health and disease in its models, including what is called "mind" with what is called "body" (papers I, II and III). Concerning its clinical utility, the technoscientific holism of systems medicine corresponds to a "holistic medicalization". Each person's whole life process – however complex – is in theory defined in biomedical, technoscientific terms as controllable, pointing towards a situation in which this whole process is underlain a regime of medical control that is holistic as in *all-encompassing*. It is directed at all levels of functioning, from the molecular to the social, continual throughout life and aimed at managing the whole continuum from cure of disease, via mitigation of risk, to optimization of health. The participatory aspect of systems medicine involves an unprecedented self-medicalization (or "participatory medicalization") where each person is expected to perform the needed self-monitoring and self-control (paper II). This profound "holistic medicalization" comes with risks of waste and harm that have so far not been judiciously addressed by the visionaries of systems medicine. It is argued that there is a philosophical and scientific discrepancy between its promises of holism and a revolution in clinical utility on the one hand and the real world complexity, unpredictability and uncontrollability of human biology on the other (papers II and III).

Discussion, conclusion and implications

The above results and arguments are further elaborated and discussed. In conclusion, systems medicine´s overarching promise of a holistic, personalized medicine that will revolutionize the clinical utility of primary care medicine is found to be associated with considerable uncertainty and a lack of focus on potential downsides. As such, it is unreliable. This raises questions as to why visionaries of systems medicine make bold promises, their ethical justification and scientific responsibility. It is argued that the philosophy of systems medicine is shaped not only according to its validity, but also its utility, and that the function of visions and promises is not only to be true or reliable, but to motivate, create positive expectations and attract social, political and economic support. However, while the creation of science visions may be necessary, they also generate actions that may have negative effects. Quaternary preventive medicine has typically lagged behind technoscientific developments. This implies a need for a more proactive, vision-focused quaternary prevention related to the

promissory aspect of biomedical science in general and systems medicine in particular. As a basis for such quaternary prevention, a less aggressive, “less is more” strategy for systems medicine is proposed.

CONTENTS

ACKNOWLEDGEMENTS

A Phd project is invariably a somewhat lonesome ride, with plenty of room for introversion, and one may easily forget whose shoulders one stands on. There are several shoulders, and looking at the list below, I feel quite proud of whom I have come to work with:

At the beginning and end of this project there is Linn, professor Linn Getz, my supervisor, who opened the doors to all of this. I would like to thank her for recognizing what potential I may have, for her willingness to initiate a Phd project, and for sharing knowledge in a wide range of topics that somehow go into this thesis. Very few academics, perhaps none other, in Norway would be willing to go for a project like this, driven by a conviction that although it may be very unorthodox and hard, it is *important*. She has the keenest eye for what is relevant, important and cutting edge in medicine. I would like to thank her for collaborations on papers and other publications in newspapers, and for countless emails and conversations, on the administrative, scientific as well as human levels. During a project that, all in all, has come to last for six years, Linn has come to mean much more to me than supervisors generally do, and she will always remain one of my most important formative figures. Last but not least I would like to thank her for her stamina, for perpetual optimism and belief in the project – even in times when it almost seemed to slip. Linn strongly believes in the powers of emergence once the initial conditions are set, and a result did emerge, there can be no doubt about that now, although it resulted from a process that was different from what we imagined in the beginning. She has given me an extraordinary freedom in shaping this project. Still: This thesis would never have been realized without Linn´s ability and willingness to see it through. Now that it is over, once the cargo of this journey is unloaded, I hope we can find new projects!

Secondly, I would like to thank professor Irene Hetlevik, my first co-supervisor, who also leads the General Practice Research Unit in Trondheim. Although Irene is not among the co-authors of the papers of this thesis, her academic focus and influence permeates them and her very keen eye for detail has improved them. However, Irene´s role is perhaps most importantly that of the silent spider, who weaves it all together and brings organizational confidence that a project like this can and will be fulfilled. She is the shoulder everybody in the General Practice Research Unit stands on.

Thirdly, I would like to thank Sara Green, philosopher of biology, who first turned up in this project as author of papers I researched (e.g. Wolkenhauer & Green, 2013). In the whole wide world this Danish scholar seemed to me the one who was working with something that most closely resembled my project. I was therefore very happy, and a little proud, to be able to collaborate with her in the latter half of the project. First, we wrote an article together in the Danish, well regarded newspaper Politiken (Green et al., 2015). Then, I was very happy to get a professional philosopher with a biomedical focus as a co-supervisor. Sara introduced be to the school of Philosophy of Science in Practice (PSP), which became a way of situating the project academically. She also validated that the project was worthwhile, and interesting, and brought a philosophical know-how to it that was critical in shaping it towards the end. In the writing of paper III, Sara also got to know me as a working partner during a process that had all the stress and creativity of a theatrical play before a premiére deadline. Next time, I will keep things on a "*kort snor*" ("short leash" in Danish), I promise!

Apart from my supervisors, my closest collaborators in this project have been my co-authors, who have also played roles akin to supervisor. First, was professor of microbiology, Elling Ulvestad, at the Haukeland University Hospital in Bergen. Elling possesses a rare combination of deep biomedical and philosophical insight, generosity and surplus that is very inspiring. He came into the work with my first article, and was instrumental in validating and helping me realize it.

Second, I was able to collaborate with political philosopher Thor Eirik Eriksen at the Arctic University of Norway in Tromsø. Thor Eirik was also very important in helping me structure the difficult *first paper*. Not least, he very literally helped me find my voice by urging me to write down what I actually wanted to say by all this. What is your agenda ("anliggende", in Norwegian) Thor Eirik annoyingly kept repeating while I was trying to focus on writing. This made me rediscover elements of my history that shape my focus. As such, Thor Eirik also made me reconstruct elements of the Prologue below. Thank you!

The third co-author is professor and medico-technologically focused philosopher Bjørn Hofmann who also became a supervisor-like person during this project. Bjørn's focus was very important in helping me realize both paper II and another paper that also sprung out of this work, but that is not formally included in this thesis (Vogt et al., 2016b). Besides bringing numerous insights to the papers, Bjørn reminded me that I do, in fact, know how to write. He

also teaches the Phd course in medical philosophy, "What is disease?" at the University of Oslo, which was also very important intellectually for this project.

At the beginning of this project, professor and researcher of children with chronic fatigue, Vegard Bruun Wyller, was also a co-supervisor. The idea was that I was to do some systems biologically oriented research in his NorCAPITAL project. The project took a different turn. However, and I find this very satisfying, we got to write a PNAS commentary at the crossroads of fatigue and omics towards the end of my project together with Elling (Vogt et al., 2016c). I feel we are not quite done here. Vegard has also very generously introduced me to his team of collaborators in Oslo, whom I also thank.

Another person who has also been important for this project is professor Anna Luise Kirkengen. Anna Luise is a very brave intellectual voice, and central to shaping the General Practice Research Unit academically. She was very important in helping me publish paper I, and also leads the Think Tank, a group springing out of the General Practice Research unit. Members here include professor of philosophy Arne Johan Vetlesen, professor of social psychology Tor-Johan Ekeland, professor of medicine Edvin Schei as well as Linn, Irene, Elling and Anna Luise herself. This is a forum to which I have been very generously invited and where I have learnt a lot. I have had illuminating conversations with all of its members. Edvin Schei also invited me to the Rosendal seminars in 2012, a very important intellectual forum, and put me in touch with Eric Cassell (see acknowledgement paper I).

Irene, Linn and Anna Luise have also introduced me to the Nordic Risk Group, trailblazers of medical critique of preventive medicine, the risk concept and overmedicalization. Among the members of this group I want especially to thank John Brodersen, professor of primary care medicine at the University of Copenhagen for important conversations. John has also been a leading figure in the ongoing Preventing Overdiagnosis project, the conferences of which I have benefitted from attending. Here, I also want to thank M.D. and Phd student Minna Johansson for inspiring conversations!

I would also like to thank my colleagues at the Department of Public Health and General Practice in Trondheim, perhaps especially professor Steinar Westin, whose 10 theses for general practice research from 1986 seem fresh even today. There are also younger colleagues that have been important to me. I want especially to thank Halfdan Petursson for sharing his experiences and insights from his project (finished in 2012) and for good conversations over a

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Additionally, there are a number of people I want to thank. Professor Per Fugelli was an important early inspiration for me back in 1997, and during this project he sent me René Dubos book "The Mirage of Health" (1959), which became an important theoretical element for me. I want to thank professor of History, John Peter Collett who, years ago during my studies of history (ca. 1999), introduced me to critical thinking about professions, science, and the welfare state. I would like to thank Associate professor Anne Kveim Lie, who teaches the Phd course in Medical History at the University of Oslo. In the intellectual deserts of Medicine, work like hers is paramount! I have also been fortunate enough to meet primary care doctor and philosopher Pekka Louhiala, who was very important in reading and validating my work with paper II. Thank you!

Early on in this project I also had fruitful conversations with biologist Astrid Lægreid and philosophers Rune Nydal and Sophia Efstathiou who also study systems biology at the Norwegian University of Science and Technology. Later on I was very fortunate to be included in Rani Lill Anjum´s CauseHealth project, to which I hope to contribute in the future. I would also like to thank Joachim Sturmberg whom I have also been fortunate to have exchanges with, especially during the Systems and Complexity Sciences for Healthcare congress in Washington, DC, 2015. Professor Sturmberg is a pioneer of (humanistic) systems thinking in medicine (Sturmberg 2007a, 2007b). Towards the end of my project, I have also been very fortunate to be invited by professor Hans-Jörg Ehni to collaborate in the "Plurality of conceptions of health" project, based at the University of Tübingen, Germany. This has both been inspiring and useful and I hope to contribute more to this project also.

There are also people who have been intellectually very important to me, although our personal interaction has been limited. I would here like to thank Eric Cassell who very generously read and commented my presentation of his philosophy (paper I). I would like to

thank systems biology and the systems biologists I have been reading. Although this is a critical analysis, the insights from their publications have still been life changing. I would like to thank professor Michael Joyner at the Mayo Clinic especially for some interesting exchanges. Especially, I would like to thank systems biologist and professor Stig Omholt at the Norwegian University of Science and Technology for illuminating conversations. Professor Omholt also put me in contact with Denis Noble himself (see acknowledgement in paper I). I would like to thank Noble for his kind responses to my requests and for his writings, which have been truly illuminating to me.

Towards the end of this project I would like to thank the The Norwegian Research Fund for General Practice (Allmennmedisinsk forskningsfond, AMFF) for funding this project. A special acknowledgement should be directed at GP Gisle Roksund for believing in this project.

Finally, I would like to thank my family. A special acknowledgement goes to my brother, Øystein, a philosopher currently publishing on issues that are also relevant to this thesis (Vogt, 2011; Vogt, 2015). Especially, I would my wife Marita who has provided all the support needed to be able to carry this through. In the end you and Olav are most important.

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Department: Department of Public Health and Nursing

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Co-supervisors: Professor Irene Hetlevik, MD, Dr. Med. and Sara Marie Ehrenreich Green, Phd.

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LIST OF PAPERS

Paper I:

Vogt, H., Ulvestad, E., Eriksen, T. E., & Getz, L. (2014). Getting personal: Can systems medicine integrate scientific and humanistic conceptions of the patient? *J Eval Clin Pract, 20*, 942–952.

Paper II:

Vogt, H., Hofmann, B., & Getz, L. (2016). The new holism: Systems medicine and the medicalization of health and life itself. *Medicine Health Care and Philosophy, 19*(2), 307-323.

Paper III:

Green, S. M. E., & Vogt, H. (2016). Personalizing medicine: Disease prevention in silico and and in socio. *Humana.Mente Journal of Philosophical Studies, 30*, 105-145.

PROLOGUE

"We have, each of us, a life-story, an inner narrative – whose continuity, whose sense, is our lives. It might be said that each of us constructs and lives a 'narrative', and that this narrative is us, our identities".

– Oliver Sacks, A Matter of Identity, 1985.

This thesis forms a milestone in of a longer story of mine, and in it I draw on several of its elements (e.g. interests and education). In line with the tradition of the humanities of making one´s own position transparent, I will here relate some of it.

I first started studying Medicine at the University of Oslo in 1997, but was only going to stay until 1998. At this point I had already had considerable experience of complex illness and disease in my near social environment. I myself had experiences with what has been known as "functional", "psychosomatic" problems or "medically unexplained symptoms", notably *tinnitus*. And although reductive biomedicine may demonstrate helplessness in demystifying these problems at the molecular or cellular scales, they turned out, at least for me, not to be unexplainable at all, neither in "biological" nor "psychosocial" terms.

The first two semesters of Medicine in Oslo were in 1997 very different from each other, reflecting a divide that reappears in this thesis: The humanities and social sciences vs. natural science. The first semester was broad and humanistic in scope, aiming to combine biomedicine with the "psychological" and "social" in the bio-psycho-social model. However, already at that time it was unclear to me how the "bio", "psycho" and "socio" actually relate in this model. Also, the "non-science" of this first semester was quickly laid aside as the second semester introduced us to the dominant force of "real medicine": Biochemistry, molecular biology and genetics. The year 1998 saw the height of expectations to the Human Genome Project (HGP). It was also the year that the term "personalized medicine" was first used in a biomedical context (Jain, 1998). In this way I was myself introduced to its genetic reductionism. Humans were no more than molecules. Lecturers would claim, for example, that a few years after the DNA sequence would be known, much disease would be "solved". In light of my previous history and the first semester, I interpreted this as a profound oversimplification and, frankly, a disconcerting disrespect of the complexity of the human

organism. At the same time, molecular biology gave me the liberating insight that the way genes work – gene expression – is dependent on their circumstances. To me, this meant that, human agents might, to some extent, change their gene expression through actions. Everybody who knows basic molecular biology may actually realize this: There is no ”bio” without ”psychosocio”, no ”nature” without ”nurture” (Alberts & Thorpe, 1998; Lewkowicz, 2011; Meaney, 2010). However, in 1998, this thinking was downplayed. In this phase of the evolving dream of biomedicine, *the molecule* reigned supreme.

Thus, I grew disenchanted with medicine. Naïvely perhaps, I contemplated the evolutionary knowledge we were taught, and concluded that medicine, by mopping up disease created by an unhealthy society, was enabling a social organization that ran contrary to evolutionary adaptations and thus would produce rather than reduce disease. I was also influenced by lecturer and professor Per Fugelli (see e.g. 2006), and works such as Aldous Huxley´s ”Brave New World” (1932), Ivan Illich’ (1975) ”Medical Nemesis” (which I found in my doctor father´s book shelves), and Danish filmmaker Lars von Trier´s brilliant medical satire ”*The Kingdom*” (1994).

In other words, I worried about *overmedicalization* (see Background, section 2.2) both regarding the expansive *holism* of the bio-psycho-social model, which has a tendency to include every aspect of life into medicine, and biomedicine, which *reduces* evermore aspects of life to molecular mechanisms and solutions that should be understood and tackled on other levels. I worried about biomedicine targeting human individuals rather than addressing environmental (social) circumstances, and what Illich termed ”cultural iatrogenesis”, that medical solutions make us forget how to understand and handle problems in non-medical ways. I worried about medicine as social control (cf. Huxley). Medicine made me profoundly uneasy, not something I could readily incorporate in my story, my identity. I took leave from my medical studies in 1998. A fellow quitting student (Dagfinn Mørkrid) and I even held a talk in class. The talk had only one slide, which I found hidden away in a box many years later (see Figure 1). I remember standing on a bridge crossing the highway outside medical school in Oslo, thinking to myself, “if only I could learn to *write* about these things”.

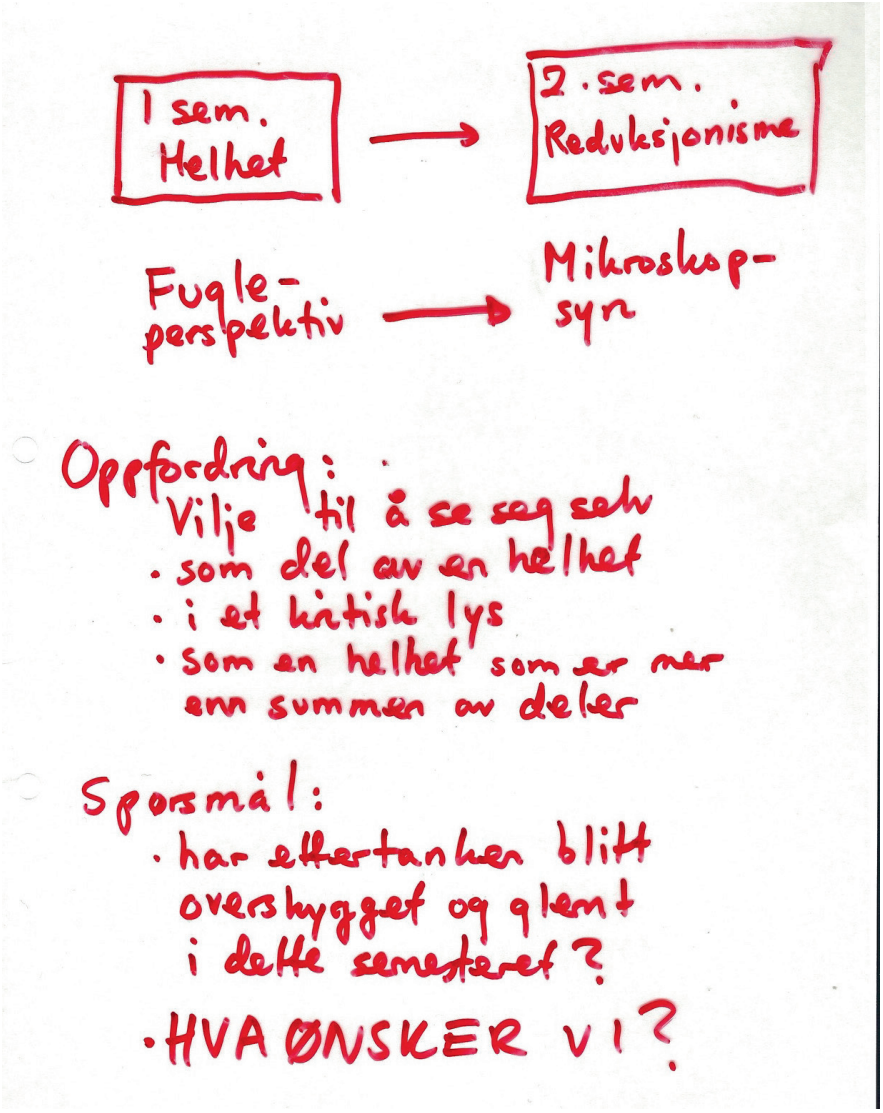

Figure 1: A scan of the slide I presented to lecturers in molecular biology and fellow students before I quit medicine as a 21 year-old in 1998: In a way that points towards this thesis, it reads:

1st semester: Wholeness → 2nd semester: Reductionism
Birds-eye perspective → Microscope gaze
Proposal:
Will to see oneself as…
- part of a whole
- in a critical light
- as a whole that is more than the sum of parts

Questions:
- has afterthought become overshadowed and forgotten in this semester?
- WHAT DO WE WANT?

After leaving Medicine, I first studied History, from 1998 to 2000, taking a course led by professor John Peter Collett at the University of Oslo termed ”*Knowledge and Power*”. The course included elements from political science and sociology in studying the history of experts, professions and the modern, scientifically based welfare state. I also briefly studied philosophy and ethics, before moving on to studying and working with Journalism in major Norwegian newspapers (2000-2003). I developed during this time an interest for the role played by history and narratives (or *stories*) in human life, not only as a means of communicating, understanding, but as an evolutionarily derived and defining feature of human biology (Christian, 2004; Sacks, 1985).

In 2003, less naïve and more pragmatic, I re-entered Medicine. I learnt to appreciate its ways, but, still ambivalent, I could not place both feet squarely within it. Throughout my studies and the following 1½ years of residency, I continued to write critical articles for magazines about medical issues. I continued to focus on overmedicalization and genetic determinism, especially in psychiatry with issues such as bipolar disorder and depression, as well as ”medically unexplained” problems (Vogt 2007b; 2008; 2009a; 2009b).

During my studies I also became interested in psychosomatics and psycho-neuro-immunology (Ader et al., 1991). From 2004 to 2007, I wrote a project thesis about the vagal nerve as an example of connections between the brain and the immune system (Vogt, 2007a). For me this work partly answered and partly pointed back towards profound questions, e.g. what assumptions underlie biomedical research, how to understand a person, how is ”bio” actually related to ”psycho” and ”socio” (i.e. the ”mind-body problem”), can human thinking and doing change molecular interactions, do we have agency at all?

Incidentally, it was also this project with the vagal nerve as an example of a new integrative or ”holistic” kind of physiology that connects the social environment and behavior to brain to (the rest of the) body that led me to my supervisor, professor Linn Getz. She shares this interest and encouraged me to develop a Phd project. The General Practice Research Unit at the Norwegian University of Science and Technology, led by professor Irene Hetlevik, has medical theory development as one key goal (Getz et al., 2007). In part this work involves the constructive introduction of concepts from other fields to support general practice. Initially, the idea was that I would follow up on my work with the vagal nerve to contribute to practice-relevant theory development on how ”biography” (the ”psychosocial”) relates to ”biology”

(observable physiological processes). From 2010, I started to prepare this project, and professor Getz introduced me to several relevant topics. Examples were social epidemiology (e.g. Marmot, 2005), social or behavioral epigenetics (McGowan & Szyf, 2010), the concept of allostasis (McEwen & Wingfield, 2003), complexity theory (Plsek & Greenhalgh, 2001; Wilson et al., 2001) and biopsychosocial, patient-centered or person-centered medicine (Cassell, 2004; Engel, 1977; McWhinney & Freeman, 2009; Starfield, 2011).

It was through this process of researching primary care relevant theory that I discovered systems biology and systems medicine. Intriguingly, it was a novelty promising not only rigorous science, but *holism* or *integrationism* and revolutions. The first work I came across was systems biologist Denis Noble's *'The Music of life'* (2006).[1] I was (and still am) deeply fascinated: It provided a biologically based, but anti-reductionist, even poetic account of the human being – very unlike medical curricula. It was this book that made me undertake this project.

Making systems medicine my topic has been immensely rewarding. Unlike molecular biology, which has relatively mindlessly proceeded to characterize the parts of the body, it was and is a philosophically very fertile field aimed at the real question: How does life really work? Through its theories and promises it highlights many, if not all, of the interests and questions I have related in the above narrative and contemporary challenges facing medicine – from the practical to the metaphysical and back. Could this systems medicine be a solution? Could it heal the divide between science and humanities, develop a holism and personalized medicine apt for medical general practice that showed how "mind" relates to "body" – "bio" to "psycho" and "socio", parts to wholes, genes to environment – and how health problems and their resolutions are actually caused? How much of human life can be accounted for by machines and computation? How would future systems medicine be in practice? And in particular: What about medicalization and overmedicalization?

As I noted on systems medicine in the protocol for this project from 2012: "This proposed ambition of an individualized, personalized, holistic and complexity-embracing medicine amounts to no less than a change in the way medicine is performed. As proposed it also may seem to assimilate or complement theory and values in general practice as formulated for

[1] Denis Noble is a renowned professor at the University of Oxford, a physiologist who pioneered computational modeling in heart physiology. He first summarized his philosophy in The Music of Life (2006).

example by McWhinney, Engel and Starfield. The question we ask in this Phd is if they actually will develop along lines that are truly “personalized” or “person-centered”. And from a thesis overview from 2013: “A fundamental goal in systems medicine is to predict and control behavior of human organisms. We ask at what cost, personally and socially, the systems medical vision of health care will come. Specifically, we question the amount of medicalization it may entail”.

Having laid aside the project on the vagal nerve, and having discovered Noble, it was with the constructive aim of introducing ”systems biology for general practice” that the present project started. From then on, it became a winding, challenging and often frustrating endeavor. Firstly, systems medicine is a moving target, which has developed as I studied it from a new and relatively unknown concept, to something much more publicized. Secondly, it became ever clearer to me that systems medicine is something as intangible as *an idea in the making*. To examine a *proposed* future framework for future medicine is not something the medical discipline provides a methodological framework for. I have had to search out and draw on a disparate set of methodological tools and theoretical perspectives. I have acquired knowledge about a wide range of subjects and fields in order to contextualize and analyze my subject (see Material and Methods section). My initial fascination with Noble and the long-drawn and challenging work of writing my first paper may also have delayed my seeing systems medicine for what it really is. However, this also means that my initial aim was not to disqualify it. At the same time the focus on overmedicalization was there from the start, and has been the subject of talks I have given throughout the project. Coming to think of it, the way I came across Noble´s book, is just as tell-tale to the nature of systems medicine as the book itself: Based on my data, it was suggested to me as a ”cure” for my questions by the algorithms of Amazon.com. Predictive machine learnt mindreading: The bright stuff of scientific dreams.

In sum, this is a project with a very broad scope. However, a broad scope is necessary for an analysis of a proposed, future framework for general practice, which addresses the whole person and a broad cultural change in medicine and society. I am not a trained philosopher to begin with, but I do believe medical doctors must traverse the borderland between theory and practice, and that developing medical theory must also involve more abstract reflections on the merits of our methods, visions of the future and their underlying philosophical assumptions.

INTRODUCTON

1. Overview and outline of the thesis

"Whether we envisage the positive expansion of knowledge and beneficent control of environment and society, or see in the systems movement the arrival of Brave New World and 1984 – it deserves intensive study, and we have to come to terms with it".

– Ludwig von Bertalanffy (1969)

This chapter provides an overview of my thesis and an explanation of how it is structured.

1.1 Overview

Almost 50 years ago, biologist and systems theorist Ludwig von Bertalanffy stated that, "if someone were to analyze current notions and fashionable catchwords, he would find '*systems*' high on the list" (Bertalanffy, 1969, p. 3). Today, the systems movement Bertalanffy referred to is finally sought realized in biology and medicine, albeit in a form influenced by the tools of our time (Chong & Ray, 2002; Drack & Wolkenhauer, 2011). The molecular biology of the past has been highly focused on individual, isolated components of the body, with limited ability to account for their interactions. After the sequencing of the human genome – the body´s "master part" – approximately 15 years ago[2], biology turned towards the complex task of *making sense of the genome* (Keller, 2005). It turned towards understanding how it interacted with other molecular constituents and how these parts are linked to the whole phenotype and its emergent properties. It turned from structure to function. In other words, it was finally ready to turn its attention from problems of reductively describing components of

[2] When was "the human genome" actually sequenced? There is no clear answer to this. A partial draft sequence was published in 2001 amid much press coverage and political limelight (Lander et al., 2001; Venter et al., 2001). However, the Human Genome Project (HGP) was not finished until 2003 and the final results were published in 2004 (International Human Genome Consortium, 2004).

the body, to the great question of biology: life itself. How does it actually work? What is it? What is living? Key to this multi-faceted endeavor is *systems biology*, the contemporary idea of which was introduced in seminal publications after the year 2000, coinciding with "mission accomplished" for genome sequencing (Aggarwal & Lee, 2003; Alon, 2003, Buchman, 2002; Ehrenberg et al., 2003; Gilbert & Sarkar, 2000; Hood, 2002; Huang, 2004; Hunter et al., 2002; Ideker et al., 2001; Kitano, 2002a; 2002b, Lazebnik, 2002, Noble, 2002; Omholt, 2002; Westerhoff & Palsson, 2004; Wolkenhauer, 2001). As the scientific ground beneath our feet is shifting with systems biology, so is the theoretical understanding of medicine, health and disease. *Systems medicine*[3] is the application of this systems biology[4] to medicine and the topic of this thesis (see Definitions and Key concepts). As shown by a search in the PubMed database, the systems medicine concept has rapidly gained traction during the last years since it first appeared 10-15 years ago (see **Figure 2**). The clinical implementation of systems medicine is often promoted as prospective or proactive *P4 medicine*, meaning predictive, preventive, personalized and participatory (Hood & Galas, 2008; Snyderman & Yoediono, 2008).

From a clinical viewpoint, it is useful to see P4 systems medicine (hereafter **P4SM**) as a part of the wider movement towards *personalized medicine* (alternatively precision medicine or stratified medicine) (Duffy, 2016; Jain, 2015). Cast as a form of personalized medicine, it is promised to pursue an ideal that is as old as the medical profession itself. There exists no single, authoritative definition of personalized medicine. To capture all forms of personalized medicine, I will very generally define it as *a form of medicine that can account for those factors that define health and disease in each particular person (i.e. variability among persons) in order to improve practice*.

But what does this concept actually mean? In the last two decades, the idea of "personalized medicine" has become the site of a somewhat quiet, but nonetheless important battle between different ideals of medicine. This battle concerns the heart of medicine. Historically,

[3] Systems medicine is also known as "systems biomedicine". "Personalized" medicine has also been known as "precision medicine", "stratified medicine", "genomic medicine", "personalized molecular medicine", "individualised medicine", "P4 medicine," "personalized healthcare" (see Duffy, 2016). It has also been called "systems pathophysiology" (Boissel et al., 2015).

[4] Systems biology may have many synonyms or strongly overlapping fields, for example computational physiology, integrative biology, integrative genetics, systems genetics, computational biology.

personalized medicine has been a humanistic and holistic medical concept in which personalization is based on the doctor knowing his/her patient as a whole person, including life circumstances, close relationships, goals and values (Mjølstad, 2015). From the 1990s and onward, scientific biomedicine has redefined this concept so that it means treating people according to their biological characteristics. However, what does "biological" mean? In the beginning of biomedical, personalized medicine, it meant according to "the genome". What has made systems medicine a particularly interesting topic for this thesis is that it promises a further redefinition of personalized medicine and *the biomedical model* itself, introducing what is envisioned as a *holistic* or *integrationist* approach (see "Model" in Definitions and Key concepts, see "Biomedical model" in Section 2.1). Such a promise of holism may seem particularly appealing to general practitioners. Primary care medicine is challenged on a daily basis with patients as *individual, whole persons*, often with complex health problems, and is therefore in need of theoretical foundation/innovation precisely in the form a personalized medicine that is *holistic*. However, while primary care doctors may at first sight welcome the idea of science-based holism, much is at stake. Traditionally, the need for holism has been met through the kind of traditional, humanistic personalized medicine mentioned above, which is grounded in the doctor-patient relationship and the idea of the patient as *a socially situated whole person* with agency, goals, experience and values. P4SM, however, is driven by technoscientific innovation, which has often been at odds with such humanistic ideals.

The ultimate clinical promise of P4SM is that its new kind of holism will enable a revolutionary shift from reactive disease-focused care to a predictive and preventive medicine that will revolutionize the overall clinical utility (see Definitions and Key concepts) of primary care medicine by keeping people healthy (Bousquet et al., 2011; Galas & Hood, 2009; Grossi, 2010; Loscalzo & Barabasi, 2011). The main clinical thrust of P4SM, the way *in which the revolution will be accomplished*, is individualized *preventive medicine*. The idea that "prevention is better than cure" is intuitively appealing.[5] However, preventive medicine has faced mounting criticism during the last years, with questions posed over its balance of benefits vs. harms/costs (see Background, section 2.2). As such, a set of pressing issues identified in primary care medicine seem to reach a "climax" with the entry of P4SM. A new framework that not only provides a new holism, but more effective preventive medicine, may

[5] Epidemiologist Geoffrey Rose's well known argument for preventive medicine was an appeal to common sense and intuition: "It is better to be healthy than ill or dead. That is the beginning and the end of the only real argument for preventive medicine. It is sufficient" (Rose, 1992, cited in Getz, 2006, p. 25).

seem to fit ”hand in glove” with the needs of primary care medicine. However, at the same time, primary care medicine is faced with the challenge of medicalization and limiting its scope.

Medicalization is at the root of criticisms towards preventive medicine (see Definitions and Key concepts). I here define medicalization as *the process by which aspects of human life come to be defined in medical terms and underlain medical control*. While medicalization and medical control are not inherently wrong, they come with risks of waste and harm, i.e. *overmedizalization*, which threaten the overall balance of benefits and harms/costs of medicine.

What the holism of P4 systems medicine actually entails, and how it will affect the overall utility of preventive medicine, are the main questions of this thesis. Its aim is to analyze this P4SM as a *proposed,* theoretical framework for future primary care medicine. Today, systems medicine exists primarily as a *prediction* about what the future will hold. This prediction is in turn based on *theoretically based arguments*. Situated in academic general practice and the medical humanities, this thesis presents an analysis of these arguments, and their underlying premises and assumptions using methods from history, philosophy and critical thinking. I seek to make these fields relevant for future planning of general practice by analysing P4SM *in light of* issues relevant for primary care medicine (see Material and Methods). I thus seek to contribute to the theoretical foundation of primary care medicine, medical professionalism, scientific responsibility and quaternary prevention. My main argument will be that P4SM redefines holism in medicine from being a humanistic to being a technoscientific concept. This holism entails an unprecedented medicalization with inherent risks. Pointing shortcomings in its holism, the risks of medicalization and previous lessons in preventive medicine, I argue that there are reasons to be skeptical of its promises of a revolution in the utility of primary care medicine.

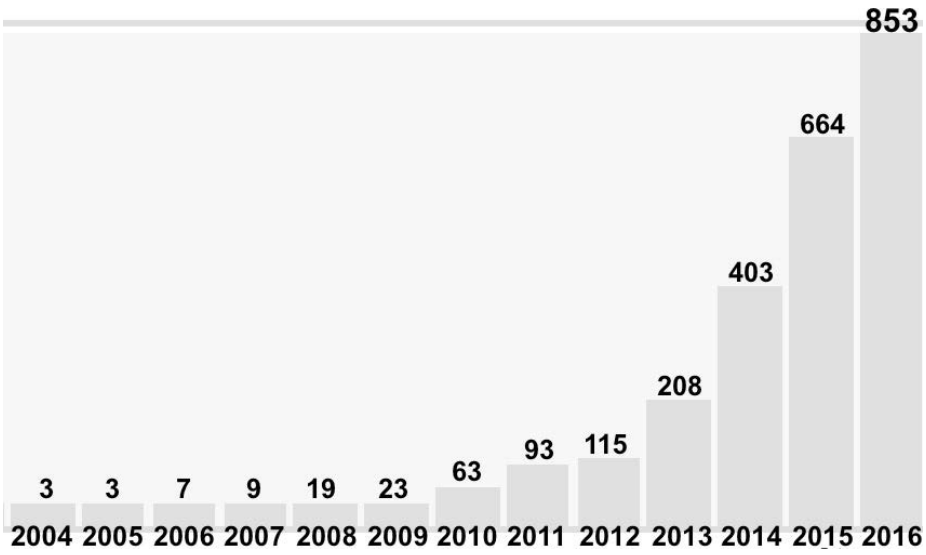

Figure 2 A search performed in the database PubMed on 2016-12-02 for (”systems medicine” OR ”systems biomedicine” OR ”P4 medicine”) illustrates the strong increase in interest in the topic of this thesis and its increasing relevance. In 2009 there were 23 hits for the first aforementioned search. The preliminary research for the present research project started in 2010. For that year there were 63 hits. The project formally started in 2012 (115 hits). For 2015 there were 664 hits. By December 2nd, 2016, there were 835 hits for this year. This shows the way the relevance of this project has increased as it has progressed.

Biologist Leroy Hood laid out the idea of systems medicine as a basis of a ”predictive, preventive and personalized” in an early lecture (2002), and published a seminal paper in *Science* in 2004 (without using the “systems medicine” term explicitly) (Hood et al., 2004). The concept of ”systems medicine” also first appears explicitly in PubMed for the first time in 2004 (Tao et al., 2004). However, the term starts to appear consistently in the literature only between 2006 and 2009, showing how the idea of applying systems biology to medicine took root at this time (Ahn et al., 2006a; 2006b; Auffray et al, 2009; Baranzini, 2006; Federoff & Gostin 2009; Liu & Kuznetsov, 2006; Liu & Lemberger, 2007; Loscalzo et al., 2007). The “P4 medicine” concept first explicitly appears in PubMed in 2008, when the ”participatory” component was added to ”predictive, preventive and personalized” (Hood, 2007; Hood, 2008, see also Snyderman & Yoediono, 2008; Hood & Galas, 2008).

1.2 Outline of the thesis and notes about its nature and structure

I will proceed as follows: This Overview and Outline (Chapter 1) constitutes the first part of the Introduction. The Introduction further consists of a Background (Chapter 2), including a historical overview, key concepts, a review of previous research and the originality of my thesis. The next main part consists of Aims (Chapter 3) and Rationale (Chapter 4). I then detail my Material (Chapter 5) and Methods (Chapter 6). I then proceed with a summary of my Results and the argument of the thesis as a whole (Chapter 7). In my Discussion (Chapter 8), I then elaborate and criticize my results and point to implications. I also discuss methodological limitations and point to future research. I then provide a conclusion (Chapter 9) and some

final remarks (Chapter 10).

Due to the unorthodoxy of this thesis in a medical context, I will first clarify some elements of its structure:

This thesis is not the typical empirical medical Phd thesis. It is a historical-philosophical analysis and argument. This means that I cross borders between two traditions. I have therefore had to make some difficult choices where these two traditions are not in perfect agreement.

Firstly, my argument builds on *premises*, some of which are presented in the Background. One important set of premises is the promises of P4SM. My being able to present these promises has in itself required considerable research and may to a certain extent perhaps be regarded as a result of my work. However, *for the sake of argument*, the historical development leading to P4SM and its promises are presented in the Background.

Furthermore, the Background chapter also contains perspectives and previous research that are in turn employed as theoretical perspectives in my analysis. As such, the contents of this background cannot be seen as entirely separate from my methods (see Section 4).

Most importantly, the fact that this thesis belongs to the medical humanities, the clear separation of ”Results” from ”Discussion” favored in the natural sciences (and therefore biomedicine) is not easy to uphold and not necessarily optimal. As explained by Lancet editor Richard Horton, modern scientific paper (or thesis) with an IMRAD setup (Introduction, Methods, Results and Discussion) is also an argument that has a direct cognate in the ancient Greek and Roman setup for an argument (Horton, 1995). This method of forming an argument is also the basis of today´s philosophy and critical thinking (Bowell & Kemp, 2015). However, the difference between the scientific and philosophical-historical paper today is that natural science clearly separates results and discussion, and imagines that while the former is purely objective, the latter is more philosophical and “free” for speculation. In natural science journals, philosophical publications (often categorized as “review”, “opinion” or “perspective”) will therefore only have introduction and discussion sections, and no methods and results (see e.g. Diamandis, 2015). In the humanities and philosophy, the pretense is not that results are purely objective. The results and conclusion – the *thesis* – is here clearly the product of philosophical-historical analyses and argumentation built on different premises – a

discussion. Still, writing in a medical context, I have here still chosen to divide my thesis quite traditionally (for biomedicine) in results and discussion. In the Results chapter, I have chosen to present a unifying summary of my papers, which together form the coherent argument that is my thesis. No additional, unpublished results, points or arguments are presented here. I then criticize and elaborate my results and argument in the Discussion. As such, one may object that there are new results or original points contained in the Discussion. However, to iterate, it is not easy to uphold a clear separation of results and discussion in this genre.

The nature of my thesis also presents a challenge regarding how to present previous research on the topic. It is not easy to clearly delineate just which past research is relevant for understanding a future framework for primary care medicine and which is not. My secondary material and background material, the "prism" through which I view my primary material (see Material and Methods), is also clearly chosen by me in an act of interpretation.

I have also studied a phenomenon (P4SM) that has continually developed along the way. Material was not gathered first, and analysis then performed second; instead material has been gathered in a piecemeal and iterative manner as the project has progressed and as my understanding of the topic has developed. The reading and analysis of this material has also been performed along the way. It is difficult to know just how much about P4SM I should be expected to have known before I started. Gaining knowledge about this topic is to a certain extent the research project. It is not a clearly delineated medical problem with an associated literature where one can presuppose that the candidate examines the state of the knowledge before formulating a hypothesis and collecting new data. This leads to the following question: How should previous research be reviewed and presented in my thesis? Somewhat confusingly, there are also conflicting advice on how to do this in a medical Phd. Holen (2013) argues that all research published up until the thesis is submitted, should be presented in the Background. Vaglum (2010) on the other hand argues that only research published before the start of the project should be presented in the Background, and that research that has appeared thereafter should be presented in the Discussion. I have opted for a middle ground. I will present all the (most relevant) research that has been published up until the end of this project, but I will divide this presentation so as to show what was published before and after I entered the Phd program. In this way I hope not only to show how original the project was when it started, but also that it presents a cutting edge argument in a context where

interest in my topic has increased. Finally, it must be said that, while some publications on systems medicine were published before I started or early in this project, I did not necessarily locate these publications until later.

2. Background

The purpose of this section is to put the emergence of P4 systems medicine (P4SM) in context and provide a historical-philosophical overview of themes, theoretical perspectives and concepts that are key to this thesis. I will also outline previous research and argue for the originality of the thesis.

- Section 2.1 describes the traditional framework of scientific biomedicine (”the biomedical model”), which, despite successes, has shortcomings that point both to challenges for primary care medicine and the advent of P4SM.
- Section 2.2 describes the challenges and needs faced by primary care medicine that arise from a conflict between its work with whole persons and biomedical reductionism. These challenges serve as focal points for this thesis.
- Section 2.3 describes theoretical solutions that primary care medicine has previously developed in meeting its need and challenges. These are medical generalism and humanistic medicine, which represent the way personalized medicine and holism have traditionally been understood *before* P4SM.
- Section 2.4 details the predictions, visions and promises of P4SM and how they seem to fit ”hand in glove” with the challenges of primary care medicine. These are the propositions and arguments that are critically analyzed in this thesis.
- Section 2.5 describes research that has previously been done in relation to my specific aim, and argues for the originality of this thesis.

2.1 The dominant framework of biomedicine

The dominant framework of scientific medicine (or “the biomedical model” [6]) is rooted in the 17th Century scientific revolution, and the worldview and method as practiced in the basic

[6] George Engel used the concept of ”the biomedical model” in a seminal paper in Science when conceptualizing the problem that he was introducing a ”biopsychosocial” alternative to (1977, p. 130). Although his description does not necessarily capture all nuances of the biomedical approach, it encapsulates its perceived shortcomings and bears repeating: ”The dominant model of disease today is biomedical, with molecular biology its basic scientific discipline. It assumes disease to be fully accounted for by deviations from the norm of measurable biological (somatic) variables. It leaves no room within its framework for the social, psychological, and behavioral dimensions of illness. The biomedical model not only requires that disease be dealt with as an entity independent of social behavior, it also demands that behavioral aberrations be explained on the basis of disordered somatic (biochemical or neurophysiological) processes. Thus the biomedical model embraces both

sciences, especially that of molecular biology and genetics (see Introduction Paper I and references therein). Its dominance is related to its success in fulfilling the goals of medicine and key tasks of unravelling cause (mechanisms), diagnosis, prediction (prognosis) and control (treatment). Medicine is a practical field, and its theoretical foundation (including ontology, epistemology and methodology, see Definitions and Key concepts) is influenced by what it can *do*; it is shaped in order for professionals to be able to act. Historically, the fundamental "tool" of medicine was the physician as a human being and his/her capacity to understand and "model" other humans through history taking and clinical examination (see Model in Definitions and Key concepts). Especially since the early 1990s, the dominant framework of medicine has also been based on testing through the statistical and population-based methods of clinical epidemiology and *evidence-based medicine* (EBM) (Greenhalgh, 2006). Crucially for this thesis, the dominant scientific framework of medicine has increasingly been based on and influenced by *technology* (Hofmann, 2002; Schlich, 2010). Technology influences the theoretical framework of biomedicine in numerous ways. Hofmann (2002 and 2014b, chapter 10) has provided overviews of how technology influences the ontology, epistemology and methods of medicine: It provides methodological access to the phenomena of the world (e.g. DNA and cells) that are otherwise unobservable and that are used for defining disease and health, both in research and clinical practice. It provides knowledge about disease and health, establishes the signs, markers and endpoints that define disease categories, and it influences systems of categorization. Fundamentally, it influences the main model of health and disease and guiding metaphors of biomedicine. For the purposes of this thesis it is also important to note that technological development also provides the impetus for generating visions and expectations as to what medicine can achieve in the future.

2.1.1 Naturalism and universalism

The dominant framework of biomedicine is *naturalist*. It is naturalist both as in adhering to the general scientific worldview "that everything arises from natural properties and causes,

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reductionism, the philosophic view that complex phenomena are ultimately derived from a single primary principle, and mind-body dualism, the doctrine that separates the mental from the somatic. Here the reductionistic primary principle is physicalistic; that is, it assumes that the language of chemistry and physics will ultimately suffice to explain biological phenomena. From the reductionist viewpoint, the only conceptual tools available to characterize and experimental tools to study biological systems are physical in nature".

and supernatural or spiritual explanations are excluded or discounted"[7], and as in the philosophy of medicine where naturalism and normativism are two key concepts:

> "According to naturalists, disease and health are descriptive concepts that can be used to define the objective and real state or condition of a person. These concepts are strictly neutral to any personal or social values. According to the normativists, however, these concepts depend upon personal and social values" (Marcum 2008, p. 63).

Epistemologically and methodologically, the dominant biomedical framework has traditionally sought *objective* knowledge. This means "public", observable, reproducible, and preferably quantifiable knowledge. Relatedly, it has tended towards *universalism*, seeking knowledge that is generalizable to all instances of a phenomenon. That which cannot be easily observed and reproduced, such as the "private" world of first-person experience, specific environmental circumstances and life history, are discounted or sought controlled for (Cassell, 2004; McWhinney & Freeman, 2009).

2.1.2 Physicalism, mechanism, reductionism, determinism

The naturalism of biomedicine has more specifically been characterized by ontological *materialism* or *physicalism* (see Definitions and Key concepts) (Marcum, 2008). More specifically, it is *mechanistic*. The heart of its conceptualization of persons, health and disease is *the machine metaphor of life* (Loeb, 1912; Thagard, 1999; Woese, 2004). A contemporary version of the machine metaphor is the information metaphor: The idea of the brain, organism or person as a complex computer processing information (McWhinney & Freeman 2009, chapter 5). The mechanism of the dominant framework is traditionally associated with causal determinism, and the related view that the future workings of the body are predictable (see Definitions and Key concepts) (Kauffman, 2008; Mazzocchi, 2008).

The mechanism of the dominant framework has also traditionally been associated with reductionism (see Definitions and Key concepts). Philosophers typically categorize reductionism as methodological, epistemological or ontological, all of which are associated with biomedicine´s mechanistic worldview (Brigandt, 2012). Methodological (or "empirical") reductionism is, quote microbiologist Carl Woese (2004, p. 174), "simply a mode of analysis, the dissection of a biological entity or system into its constituent parts in order better to understand it". Medicine is pragmatic. Methodological reductionism, spurred by technologies

[7] Oxforddictionaries.com, accessed 2016-05-10

providing access to the parts of the body, has been a successful strategy for *simplifying* the enormous complexity of personal health to something mechanistically explainable, measurable, predictable and controllable (or "actionable", see Definitions and Key concepts). Methodological reductionism needs not have any metaphysical strings attached. However, in practice it is associated with a worldview where "living systems (like all else) can be completely understood in terms of the properties of their constituent parts" (Woese, 2004, p. 174). *Ontological reductionism* (or "smallism", see Paper I) is the metaphysical belief in the universal applicability of *upward* causation that causality flows from the mechanistic interactions of small, fundamental entities (i.e. molecules) to fully determine the whole in all its complexity (see Definitions and Key concepts for "complexity", see also McWhinney & Freeman, 2009, chapter 5; Woese, 2004). The biomedical model has thus typically promoted a disease-focus where diseases are tied to abnormalities in bodily parts, and where not only "somatic", but also "psychosocial" problems can in theory be explained *in terms of parts* (Engel, 1977; McWhinney & Freeman, 2009, Chapter 5; Velmans, 2009).

2.1.3 Linearity and etiological specificity

The reductionism of the biomedical model has also been associated with what can be called *linearity* (as opposed to non-linearity, which is tied to ideas of *complexity*, see Definitions and Key Concepts) (Borrell-Carrió et al. 2004; Woese, 2004). It would be straw man argumentation to claim that biomedicine has not realized that bodily interactions are complex. However, because of methodological and technological limitations, biology has not been able to investigate or know the complex organization and development of the body. Instead, its tools have spurred it to reduce the complex to relatively simple, linear causal chains. The resulting "linear" (or "one-to-one") view of health and disease is associated with a belief in *etiological specificity*, which in its extreme form states that, "each disease has a specific causal agent" (McWhinney & Freeman, 2009).

As the above described biomedical model dominates medicine, it is also intimately linked to its shortcomings and the challenges of primary care medicine.

2.2 The challenges and needs of primary care medicine

This thesis is about systems medicine as a proposed theoretical framework *for primary care medicine* (general practice or family medicine). What makes primary care medicine "primary" is that it is the first point of contact for the patient seeking help. What makes it "general" is that, unlike specialties focusing on bodily subsystems or single diseases, it is defined by the generalist clinical challenge of providing the best possible, tailored care for individual, whole persons in all their complexity, presenting previously uncategorized health problems (Greenhalgh, 2007; McWhinney & Freeman, chapter 2; RCGP, 2012).

The challenges of primary care medicine are strongly tied to health problems it must deal with. This panorama has gradually shifted towards non-communicable, chronic (long-term) and costly health problems, the complexity of which is highlighted by two phenomena: *multi-morbidity* and so-called *medically unexplained symptoms* (see paper I and Austad et al., 2016; Burton, 2004; Eriksen et al., 2013a; 2013b; Parekh & Barton, 2010; WHO, 2008). Both conceptual work and empirical evidence on chronic health problems, multi-morbidity and MUS have led to calls for a shift from such a disease-focused reductionism to a personalized or person-centered approach that is *holistic* and transcends the *fragmentation* that characterizes biomedical care of patients with complex health problems (Barnett et al., 2012; Eriksen et al. 2013a; Mangin et al., 2012; Parekh & Barton, 2010; Pefoyo et al., 2015; Tomasdottir et al., 2014; 2015; WHO, 2008).

In this thesis I will thus define the overarching theoretical challenge of primary care medicine as the need to develop:

> **A theoretical framework (ontology, philosophy of causation, epistemology and methods in research and practice) that can counteract fragmentation and account for the complexity of health and disease in the whole, environmentally and socially situated person over time and that promotes a sustainable and responsible practice, with the best possible overall utility (i.e. the balance benefits vs. harms/costs in the widest sense). This must involve the setting of boundaries for what medicine can and should do, that is limits to defining aspects of life in medical terms and putting them under medical control (i.e. self-limitation of medicalization).**

This does not of course cover *all* the challenges of primary care medicine (see e.g.

Greenhalgh, 2007), but serves in this thesis as the real-life trials that systems medicine must stand up to as a strategy for primary care. By utility in the "widest sense" I mean not only easily quantifiable effects on the individual and population level, but also effects on the individual level and societal level that may be hard to quantify, but yet professionally and ethically important.

In the following I will divide the overarching challenge of primary care into three sub-challenges that will reappear later in the thesis: Fragmentation, overall utility (i.e. the balance benefits vs. harms/costs in the widest sense) and medicalization.

2.2.1 The challenge of fragmentation

> *"The crippling flaw of the (biomedical) model is that it does not include the patient and his attributes as a person, a human being"*
> – *George Engel (1980)*

As it deals with whole persons over time, primary care medicine is by nature in need of a personalized medicine that is also *holistic* (Greenhalgh, 2007; McWhinney & Freeman, 2009).[8] General practice entails "situations where the whole is more than the sum of the parts" (Stange, 2009b). At the same time, the dominant scientific framework of biomedicine entails *universalism* and *reduction*. The result is *depersonalization*. Depersonalization can be said to have two aspects: Universalism "one-size fits all" and fragmentation.

Universalism or "one-size-fits-all medicine", which treats the person as an averaged individual, is the flip side of scientific medicine´s quest for generalizable, objective knowledge (Cassell, 2004; Kelly et al., 2015). All attempts at personalizing medicine are essence attempts to counteract universalism.

Fragmentation (or *disintegration*) results from the dominant framework´s reductionism and linear thinking. It is also intimately tied to "one-size-fits-all" medicine all the time one cannot

[8] One could of course argue that primary care medicine *does not* need to develop any holism, and instead deal with the sum of bodily parts and their diseases, each of which is the focus of a medical speciality. However, that would mean a generalist discipline with no generalist theory for the phenomenon that defines it, *the whole person*.

meaningfully describe an individual unless one considers that person as a whole. Fragmentation is thus a key hindrance to personalization. It is also perceived as a key impediment to clinical utility. As a premise for the present argument, fragmentation can thus be cast as *the* main theoretical challenge of contemporary primary care medicine (Getz, 2001; Elhauge, 2010; WHO, 2008). An Annals of Family medicine editorial encapsulates this view:

> "Underlying the current healthcare failings is a critical underappreciated problem: fragmentation— focusing and acting on the parts without adequately appreciating their relation to the evolving whole. This unbalance, this brokenness, is at the root of the more obvious healthcare crises of unsustainable cost increases, poor quality, and inequality. Fragmentation is at the heart of the ineffectiveness of our increasingly frantic efforts to nurture improvement. Knowledge advanced greatly in the modern era by making sense of complicated things by understanding their parts. The ensuing rise in specialization has led to breathtaking advances from isolating, partitioning, and manipulating the components of physical, biological, and human systems. (…) Specialized information has expanded without a similar expansion in our ability to integrate, prioritize, and personalize narrowly construed information. As a result, our ability to turn information into knowledge and knowledge into wisdom has diminished" (Stange, 2009a, pp. 100-101).

The challenge of fragmentation thus has several aspects: The focus on isolated bodily parts and linear mechanisms results in a conceptually disintegrated body. Ontological reductionism and the idea of upward causation downplay the importance of wholes, and cause the framework to reduce "the mind" to bodily parts (see Paper I). A major challenge for primary care medicine is thus to link "bio", "psycho" and "socio" in the biopsychosocial model: To account for the (causal) relationship between what we call "psychosocial" (the experience, agency and behavior of whole persons) and the "biological" as in molecular, cells and organs in health and disease.

2.2.2. The challenge of overall utility, especially in preventive medicine

In its quest for usefulness and beneficent control of human life, medicine has historically moved from a focus on the person´s illness experience or parts-associated disease in the "here and now" towards another main focus: Disease in the future and predictive and preventive medicine. Today, primary care is where most individual-centered predictive and preventive medicine takes place, making this a major academic and clinical challenge of primary care medicine (Getz, 2006). As the promises of P4SM are also strongly dependent on preventive medicine it is a main focus of this thesis.

The central concept in predictive medicine is *risk* (or *susceptibility*) (Lupton, 2013; Skolbekken, 1995). The fundamental problem of life that it seeks to overcome is *uncertainty* (Cassell, 2004). The need to make predictions is essential in life as it enables us to know what will happen and thus what to do. It enables control. The prerequisite is some form of *predictive modeling* (see Definitions and Key concepts).

Instead of repeating myself, I refer the reader Paper III for a description of the challenge of clinical utility, especially in preventive medicine. In brief, its success must be measured as relative to the problems it tries to solve, its expansiveness, costs and harms. In the past two decades there has been an increasing focus on the downsides of preventive medicine (Getz, 2006; Godlee, 2005; Sackett, 2002; Starfield et al., 2008; Verweji, 1999, see also BMJ; JAMA Internal Medicine). Today, preventive medicine may be seen as standing on a tipping point where waste and harm threaten to outweigh the benefits. This challenge is related to fragmentation and medicalization.

In sum, primary care medicine is in need of theoretical innovation. This leaves a door open for P4SM.

2.2.3 The challenge of medicalization

In order to achieve a best possible balance of benefits vs. waste and harm, primary care medicine needs – by necessity – to set boundaries for its own expansion or medicalization, which always comes with dangers of overmedicalization.

I have defined medicalization as "*the process by which aspects of human life come to be defined in medical terms and underlain medical control*" (see also papers II and III). A few words on this definition: Firstly, I have chosen the term "aspect of life" to open up the concept for the fact that the process of medicalization does not only involve control of phenomena that are considered problems in the first place. It also focuses on different aspects of the body, from molecules to behavior, as well as healthy states. Secondly, the reason I choose the word "control" as opposed to "jurisdiction" or "authority" (also often used in other definitions) is because the word "control" corresponds better to what biomedicine is actually doing and seeking. Biomedicine's key goal of *control* over life processes is clearly key to medicalization. The term "control" is useful as a common denominator that can be understood

across professional boundaries. It is my view that the control sought by biomedicine is essentially the same control that social scientists perceive as "authority", "jurisdiction" or political/social control over people´s lives. The idea that medicine can be used for social control, presupposes that biomedicine has found (or is assumed to have found) effective ways to control life at the level of individual bodies and their parts.[9] In a sense, I understand medicalization in the same way as the biological sciences understand control in terms of "organization" of life, which includes social organization. Medicalization is the way human life becomes organized in medical ways.

Thirdly, although the term medicalization has often had a pejorative meaning, my description is intended as descriptive and not inherently negative (see e.g. Conrad, 2007 for such a view). The way I frame it, medicalization is a reconceptualization of the way medicine steadily increases its control the human body and the whole realm of human living. In this way, medicalization is the biomedical project. *Beneficient control* is a prime goal of biology and medicine. To paraphrase a catchphrase for biomedical, personalized medicine, the aim of medicine is to "*medicalize the right health problem, at the right time, every time, in the right person*".[10]

However, all medicalization (like all attempts at taking control) comes with a potential for waste and harm, i.e. *overmedizalization*. This threatens the overall balance of benefits and harms/costs of medicine. Such risks are both direct iatrogenic harm (e.g. anxiety and side-effects of unnecessary medications) and costs and indirect harm and costs resulting from missed opportunities that could have been realized through the lost resources (opportunity cost). Key concepts in understanding overmedicalization are overdiagnosis, false positives and false negatives.

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[9] Scientists do not use the terms jurisdiction or authority, but they do use control. As an example, engineers and systems biologists refer to "control theory", which is related to cybernetics. Control is a key aim of the life sciences. "Bios" is originally Greek meaning "life", and the suffix "logy" (as in "logos") means theory or science. Biology thus means "the theory or science of life" (discussed by Downing, 2011, p. 2, see also Kohl & Noble, 2009). Biology is fundamentally aimed at a scientific theory of life itself, and of explanation, prediction and potentially control of the whole life process. This point is underscored by the pivotal 19th Century biologist Jacques Loeb (1859–1924), who can be seen as central to the engineering ideal in biology: "It is possible to get the life-phenomenon under our control (...) such a control and nothing else is the aim of biology— (cited in Pauly 1987, p. 174, see opening quote Paper II).

[10] The original catchphrase comes in many variants. US President Barack Obama states, for example, about precision medicine that it is about "...delivering the right treatments, at the right time, every time to the right person" (cited in Duffy, 2016, p. 1).

Medicalization is a vast topic that cannot be covered comprehensively here, and I refer the reader especially to my paper II, references therein and authoritative reviews (Clarke et al., 2010; Conrad, 2007; Maturo, 2012). In this thesis, I call the contemporary process of medicalization that is most relevant for understanding P4SM "the medicalization of health and life itself". I here rely especially on the concepts of *biohealth* (Downing, 2011), *biomedicalization* (Clarke et al., 2010) and *biopolitics* (Rabinow & Rose, 2006; Rose, 2001; 2007), but also on *surveillance medicine* (Armstrong, 1995), *social and cultural iatrogenesis* (Illich, 1975) as well as *overdiagnosis* (Welch et al., 2011), and a number of other publications. In particular, I employ the perspectives of primary care physician and philosopher Raymond Downing.[11] What I call the medicalization of health and life itself (and Downing calls "biohealth") is strongly associated with predictive or preventive medicine, which is also in an important sense *holistic*, as it focuses on the whole, temporal life process. While curative (or "disease-focused") medicine deals with already sick people, individual-centric preventive medicine deals with asymptomatic or healthy people, for instance through screening. In order to prevent something, one here has to take control over aspects of life at a time-point when one is not having the problem, thus medicalizing them.

2.3 Past holism: Medical generalism and humanistic medicine

> *"The person has become the subject and object of contemporary medicine*".
> - Eric Cassell (2013)

How has primary care medicine previously attempted to deal with the above described challenges? How has it tried to provide personalized medicine and *holism,* and how have these concepts been understood before P4SM? The answer is, first and foremost in terms of *medical generalism* and *humanistic medicine*.

[11] I see Downing´s work as usefully summing up a large literature, as he builds on and refers to a number of other authors, notably Arney & Bergen (1984) who referred to "the management of the living". Nikolas Rose more recently called it "the management of life" (Rose, 2001), Clarke et al. (2010) coined the term "biomedicalization", and Ivan Illich called the society in which it takes place a "brave new biocracy". Other scholars have named vital elements of this concept. For example, Robert Crawford (1980) referred to "healthism" and David Armstrong to "surveillance medicine" (Armstrong, 1995) (see Downing 2011, p. 7). Skolbekken (2012) also refers to "the medicalization of everyday life".

2.3.1 Medical generalism

Medical generalism can be viewed not only as a key to professionalism in primary care medicine, but as *a philosophy* (McWhinney & Freeman, 2009; RCGP, 2012). As an example of how it is linked to holism, the Royal College of General Practitioners in England states that, ”Generalist knowledge is characterised by a perspective on the whole rather than the parts, on relationships and processes rather than components and facts; and on judicious, context-specific decisions on how and at what level (individual, family, system) to consider a problem” (RCGP, 2012, p. 7; citing Ian McWhinney). This philosophy is defined and enabled by the ”tools” the doctor-patient relationship provides over time (Fugelli & Heath, 1996; Mjølstad, 2015). It is grounded in the ability of the doctor, as a specially trained human being, to *model* the patient as a whole person, integrating various fragmented information, and thus *personalizing medicine* to enable to make predictions about what is best for that person there and then (Cassell, 2004).

2.3.2 Humanistic medicine

The philosophy of medical generalism roughly corresponds to what has been called *humanistic medicine* (Marcum, 2008, see Paper I). Humanistic medicine denotes a stream of medical thought and practice that is based on a conceptualization of the patient as a whole person, and not only parts-associated diseases (Marcum, 2008, p. 10). Today, a range of proposed frameworks and approaches can be placed under the umbrella of “humanistic medicine” (see footnote[12]). Engel´s biopsychosocial model[13] (Engel, 1977; 1980) and patient-centered medicine (McWhinney & Freeman, 2009) are the most widely known, but the current movement for *person-centered medicine* is perhaps the clearest example (Miles & Mezzich, 2011). It has also simply been called *medical holism* (Kunitz, 2002) and *personalized medicine* (Gibson, 1971).

[12] Frameworks that I would place under the umbrella of “humanistic medicine” include “biopsychosocial medicine”, “biographical medicine” (Armstrong, 1979), “context-sensitive medicine” (Greenhalgh et al., 1997), “interpretive medicine” (Reeve, 2010), “life-world led healthcare” (Todres, 2007), “medical phenomenology” (Gergel 2012), “narrative-based medicine” (Greenhalgh, 1999), “patient-centered medicine” (Weston, 2005), person-focused care (Starfield, 2011); person-centered medicine (Cassell 2004, 2010, 2013; Miles & Mezzich, 2011; Robinson, 1939; Sturmberg, 2009).

[13] It should be noted that biopsychosocial medicine is a concept that has been used by a number of authors (e.g. Wessely et al., 2005), and may sometimes be taken merely to be an inflated version of the biomedical models, applying the same scientific philosophy and methods on all levels. I refer to it as originally proposed by George Engel (1977, 1980, 1997; see also Borrell-Carrió et al., 2004).

Humanistic medicine is defined by its idea of what a person is. I have drawn especially on Eric Cassell (see paper I) as a source of systematic thinking on the subject and object of medicine. He summarizes his conceptualization thus:

> "A person is an embodied, purposeful, thinking, feeling, emotional, reflective, relational, human individual always in action, responsive to meaning, and whose life in all spheres points both outward and inward. Virtually all of a person's actions—volitional, habitual, instinctual, or automatic—are based on meanings. Persons live at all times in a context of ever present relationships in which a variable degree of trust is necessary both in others and in the self" (Cassell, 2010, p. 50).

It is through this kind of model of the person that medical generalism and humanistic medicine seeks to counteract fragmentation and achieve the best possible overall utility and quality of care (i.e. balance of benefits and harms) (Getz, 2006).

Regarding the challenge of medicalization, this form of holistic, personalized medicine has traditionally emphasized a low-tech approach and taken a critical stance towards medicalization (Borrell-Carrió, 2004, p. 580; see also, Downing, 2011; Forssén et al., 2011; Getz, 2006; Jamoulle et al., 2015). Humanistic medicine and medical generalism has in general been associated with a certain tolerance towards uncertainty, the inevitability, unpredictability and uncontrollability of disease and death (Callahan, 1998; Cassell, 2013, Fugelli, 2006; Fugelli & Heath, 1996, see Definitions and Key concepts for "predictability" and "prediction"). Unlike the biomedical model, it has also emphasized that a state of good health may be compatible with presence of disease and risk factors.

I would here also like to note that the term "humanistic medicine" is not unproblematic. I should underscore that I do not mean that technologically based and scientific biomedicine is inherently *non-humanistic*, as natural science is in fact a crucial part of the humanistic project since the renaissance and use of technology a defining feature of human nature (Christian, 2004; Wifstad, 2007). However, what the concept of humanistic medicine reflects, is the perception that scientific biomedicine cannot account for the person as a whole. Humanistic medicine seeks to integrate natural science, but also to expand its scope, drawing on the philosophy and methods of the social sciences and humanities (Cassell, 2014; Cole et al., 2014; Gergel, 2012; McWhinney & Freeman, 2009; Miles & Mezzich, 2011).

It should also briefly be noted that P4SM is by no means the first instance where systems thinking influences primary care medicine. Conceptual tools and metaphors for systems

theory, complexity theory[14] and system-oriented ”organismic” biological theory have previously been employed to scientifically underpin the holism of humanistic medicine and its idea of personalization (Khusfh, 2008; Heath, 2013a, see also Definitions and Key concepts for “organicism”). This amounts to a little known ”humanistic systems medicine”. The most wellknown examples are Engel´s and McWhinney’s use of Ludwig von Bertalanffy´s general systems theory and organismic biology in developing the biopsychosocial model and patient-centered medicine, but there are numerous others (Engel, 1977; 1980; McWhinney & Freeman, 2009, Chapter 5, see also Borrell-Carrió et al., 2004; Plsek & Greenhalgh, 2001; Sturmberg 2007a, 2007b; Sturmberg et al., 2014; Wilson et al., 2001).

2.4 The promises of systems medicine

In the following I will present the promises made by advocates of P4 systems medicine. Tantalizingly, they correspond to the challenges faced by primary care medicine.

2.4.1 The promise of holism and integration

P4SM represents a continuation of *biomedicine´s* promise of a new, scientific and technologically based personalized medicine, which originated with the sequencing of the human genome (Kevles & Hood, 1992; Subramanian et al., 2001). In the following, I will first present this *genomic medicine* and then present personalized *systems medicine* (P4SM) as an extension of its promises.

I have defined *personalized medicine* as a medicine that can account for those factors that define health and disease in each particular human being or person in order to improve practice (see Overview chapter). Very generally, *the act of personalizing* medicine lies not only in characterizing the person or his/her condition in detail through various means; *it lies in what model you compare the individual to* (see Model in Definitions and Key concepts). For example, if you want to predict whether a particular individual will come to develop

[14] Complexity theory is related to the systems theory employed in systems biology and I will treat complexity theory and systems theory synonymously in this thesis. They both seek to describe and define complex systems.

diabetes, you need to discover some pattern in that person that corresponds to a pattern in a pre-established model of someone who develops diabetes. In the traditional, dominant framework of biomedicine and evidence-based medicine, information about each person has been compared to models of the "universal" or "average" patient derived from epidemiological studies with large and often non-stratified populations. The result is depersonalization in the form of "one-size-fits all" medicine. The traditional humanistic personalized medicine (outlined in the last section) attempted to personalize medicine by accounting for personal characteristics such as personal experience, goals, values and social relationships with a "holistic" model based on the doctor´s previous experience with that person, as well as scientific knowledge and other experience.

The term "personalized medicine" was first adopted in a scientific, biomedical context around the year 2000 (Jain, 1998; Langreth & Waldholz, 1999; Mancinelli et al., 2000).[15] How was personalization understood in this early *genomic personalized medicine*? Here, "those factors" that define each particular person was typically *DNA alone* (Gross, 1994). The main strategy of early, gene-centric biomedicine was first and foremost to counteract universalism through *stratification*. Stratification means dividing patient populations or disease phenotypes into smaller groups ("strata") by aggregating those sharing some essential pattern. Instead of comparing individual data to a large heterogeneous population, *personalization* here means comparing the individual patient to a population, which is as similar to the patient as possible. In genomic – or gene-centric – personalized medicine, the main strategy has been to stratify people and diseases into smaller groups according to genetic characteristics, and then to compare individuals to with other cases with a similar DNA profile.[16] In the 1990s, key proponents of genomically based personalized medicine promised that personalization would yield a revolutionary, more precise medicine with individually tailored treatments (Gilbert, 1992, p. 94; Hood, 1992, p. 163; Hjorleifsson and Schei, 2006). Accounting for an individual´s genes would lead to improved predictive power and more efficient preventive control of common conditions (Collins et al., 2003).

[15] The idea of a scientifically based personalized medicine was present early in the human genome project (Kevles & Hood, 1992).

[16] For this reason, some authors prefer the term "stratified medicine" to "personalized medicine".

However, in the years that followed, this revolution in medicine did not pan out *as promised*. The revolution was *postponed* (Hall, 2010). Why? One should be careful with the straw man of genetic reductionism and determinism. However, *the promises* (as opposed to more cautious thinking, see Discussion, Section 7.5) of early genomic personalized medicine still seems to have been associated not only with methodological reductionism, but an epistemological and ontological primacy of the genome that rendered the whole phenotype easily predictable (De Backer et al., 2010; Keller, 1992; 2000; 2005; Newman, 2003; Strohman, 1993). The focus of molecular biology was on genes (as in specific DNA sequences), and relatively simple mechanisms between genes and phenotype (Darden & Tabery, 2009). Very generally, what became increasingly clear during the decade after the Human Genome Project was that the relationship between the parts (genome and molecules) and the environmentally embedded phenotype (the whole person, health and disease) was far more complex than what the promises relied on. Here I refer the reader to descriptions in my papers, footnote[17], and the following references as examples of literature treating this topic (Caspi et al., 2006; Chakravarti, 2011; Check Hayden, 2010; 2016; Editorial Nature Biotechnology, 2012; Keller, 2005; 2014; Gratten & Visscher, 2016; Hall, 2010; Kaiser, 2012; Lewkowicz, 2011; Maher, 2008; Meaney, 2010; Noble, 2010; Phillips, 2008; Rose, 1997; Thanassoulis & Vasan, 2010; Turkheimer, 2011; Wright & Hastie, 2001). While pioneers of the human genome project may have appreciated that the human organism is complex (see e.g Sulston & Ferry, 2002), it was at least in the *rhetoric* of biomedicine "news"

[17] In particular, the then popular "common disease–common variant hypothesis", i.e., that common, specific genetic variants could explain and predict common diseases has, in general, proved to be an oversimplification (Hall, 2010; Joyner & Prendergast, 2014; McClellan & King. 2010; McPherson, 2016). That it was likely an oversimplification was known among biologists from the start of the HGP, but it was an unpopular view held by a "negative" minority (Rose, 1997; Wright & Hastie, 2001). Another related problem is "missing heritability": That summing up the effects of known genetic variants contributing to a disease only explains a small portion of its heritability (Zuk et al., 2012). Missing heritability may be due to gene-gene interactions (epistasis), gene-environment interactions, or perhaps rare variants with large effects. Evidence has mounted for widespread pleiotropy, meaning that individual DNA variants influence multiple phenotypes, often in unexpected ways (Gratten & Visscher, 2016). As Darden & Tabery noted in (2009), "genomics itself is wrestling with the complexities posed by how a mere 20,000 genes can construct a human while a grain of rice requires 50,000 genes". A DNA-centric view of biology may also have been strengthened by The Central Dogma of molecular biology developed by Francis Crick, which states that information flow from genome to protein is one way (Joyner & Prenderfast, 2014). As an example of the philosophy expressed in the promises at the time, Hood (1992) stated that, "For each defective gene there will be therapeutic regimens that will circumvent the limitations of the defective gene", clearly a statement that assumed a simple, linear relationship between genotype and phenotype. Remarks made by molecular biologist and Nobel laureate Walter Gilbert also illustrate this point. Although he warned against what he called "shallow genetic determinism", he noted in 1992 that "Three billion bases of sequences can be put on a single compact disk (CD), and one will be able to pull a CD out of one's pocket and say, 'Here is a human being; it's me!'" (Gilbert, 1992, p. 84). The way Gilbert conceptualized the body, "genetic information" was "the most fundamental property".

when a *Science* editorial in 2011 stated that, "The lessons from genome biology are quite clear. Genes and their products almost never act alone, but in networks with other genes and proteins and in context of the environment" (Chakravarti, 2011).

At the same time, the sequencing of the human genome not only offered disappointments; it also offered progress and new technological opportunities. The last 15 years have seen an increased capacity to generate not only genomic data (DNA sequence), but other "omics" data on other molecular constituents of the body; epigenetic markers or "epigenome", RNA or "transcriptome", protein ("proteome") and "metabolites ("metabolome"), etc., (see Definitions and Key concepts for "omics"). Various other technologies for gathering "big data" on the human phenotype ("phenomics") and environmental exposures ("exposomics") have also been developed (see Definitions and Key concepts). Some of these (e.g. sensors and mobile phones) are easily accessible, allowing consumers to measure themselves, a development that is highlighted in "quantified self movement" (Wolf, 2009). A third source of data is electronic health records. At the same time, novel computational power has emerged, enabling attempts to integrate, analyze and *make sense of* these data.

Systems medicine arises from these opportunities as well as the limitations of previous genomic medicine. It represents a watershed in the history of biology. While molecular biology was more descriptive, systems biology is an integrative *sense-making endeavor*. It is biomedicine transitioning from characterizing components and generating data to interpretation of what it has discovered in the last decades. Molecular biology discovered the fragmented characters of the alphabet. Systems biology and medicine is to write the story of life and health.

How to do this scientifically? Systems medicine is a form of computational *("in silico")*[18] medicine. There are many attempts to make sense of big data through computation. What defines systems medicine is its emphasis on mathematical or computational modeling of human biological systems *as complex systems*. It reflects a recognition that personalized biomedicine needs to study biological entities in terms of *wholes,* guided by some form of

[18] The term "*in silico*" refers to silicone, which is a key constituent of computers (as in "Silicon valley"). *In silico* biology and medicine means biology and medicine that employs computational modeling in research and the clinic.

systems theory (Boogerd et al., 2007 eds; O'Malley & Dupré, 2005; Noble, 2006; Thomas, 2007).

As noted in my above discussion, all the P's in "P4" medicine (predictice, preventive, personalized and participatory) were present from the start of the Human Genome Project (Kevles & Hood, 1992). What is new, and the key theoretical promise of systems medicine – *the promise on which all its other promises hinge* – is that it will take biomedicine and personalized medicine from a reductionist to a *holistic* philosophy and practice and connect the parts to an idea of the whole. While early *genomic* personalized medicine attempted to personalize medicine by counteracting universalism, it did little to counteract *fragmentation*. In systems medicine the name of the game is *integration* and counteracting fragmentation. In an emblematic paper, a large number of prominent systems biologists[19] sum up the promises of systems medicine as follows:

> "Healthcare often focuses on single diseases, advanced technology, biomedical interventions and specialist care. (...) Fragmenting care can reduce the ability of primary care clinicians to ensure that patient care is comprehensive, integrated, holistic, and coordinated (…). Thus, we propose that NCD management should move towards holistic multi-modal integrated care, and multi-scale, multi-level systems approaches. To reduce their socio-economic and public health impacts, we propose that NCDs should be considered as the expression of a continuum or common group of diseases with intertwined gene-environment, socio-economic interactions and co-morbidities that lead to complex phenotypes specific for each individual. The 'systems medicine' concept, which takes a holistic view of health and disease, encapsulates this perspective. Systems medicine aims to tackle all components of the complexity of NCDs so as to understand these various phenotypes and hence enable prevention, control through health promotion and personalized medicine, and an efficient use of health service resources. It does this through integrated care using multidisciplinary and teamwork approaches centered in primary and community care, including the essential ethical dimension" (Bousquet 2011, pp. 3-5).

As such, systems medicine also seems to take personalized biomedicine into a rhetorical space that has previously been occupied by the holism of "humanistic medicine": To develop a "holistic personalized medicine" that tackles the complexity of the whole person. This is just what primary care medicine seeks.

[19] To underscore the impact on and relevance for primary care of this publication, it should be noted that, among 64 authors was the President (at the time) of the World Association of Family Doctors (WONCA), Richard G. Roberts.

2.4.2. The promise of a revolution in overall clinical utility

Above I have described the key conceptual and methodological promise of P4SM: A holistic framework that will counteract fragmentation in medicine and make sense of all the big data pertaining to a person. The main clinical promise of P4SM is a revolution in the overall utility of medicine (e.g. better balance of benefits vs. harms and costs), especially predictive and preventive medicine, *through this holistic approach* (Bousquet et al., 2011; Galas & Hood, 2009). This promise is strongly related to the expectation that it will enable increasing predictive power (more accurate algorithms for assessing disease risk), more accurate methods for detecting disease at an early stage, and subsequently more effective disease prevention (Snyderman & Yoediono, 2008).[20] It also rests on the expectation that affordable, wearable technology will enable a participatory medicine, which will democratize the field and empower individuals to take control over their own life and health through access to personalized information (Hood & Galas, 2008; Tian et al., 2012).

In sum, the promises of P4SM may seem to fit "hand in glove" with the theoretical needs of general practice.

2.5 Previous research and originality of the thesis

In the following, I will review previous research that has specific relevance to the aim of this thesis (see Section 1.2 for notes about its structure). I will then argue for its originality.

[20] Bousquet et al. (2011), for example state that, "Using methods used in non-medical complex model systems, it should be possible to monitor 'early warning signals', which predict the state of disease progression". In an early lecture, Leroy Hood (2002, p. 27) stated in a lecture: "My prediction is that in 10-15 years, we will have identified hundreds of genes that predispose to disease. We will be able to analyze the relevant DNA sequences from these genes from a small amount of blood and use these to predict a probabilistic future health history for each individual. This is predictive medicine. Since it is an anathema in medicine to predict without being able to cure or prevent, we will use systems approaches over the next 15-25 years to place these defective genes in the context of their biological systems and learn how to circumvent their limitations. This is preventive medicine. The agents for preventive medicine will include drugs, embryonic stem cell therapy, engineered proteins, genetically-engineered cells, and many others. Because each of us will have different potential disease combinations, medicine will become highly personalized. My prediction is that preventive medicine will extend the average lifespan by 10-30 years".

2.5.1. Research on concepts and methods in systems biology/medicine

With regard to systems biology´s conception of living systems and methods, a number of publications had been published by 2012 outlining its historical roots, philosophy, different schools of thought and practice, and their limitations (Boogerd et al., 2007 eds; Calvert & Fujimura, 2011; De Backer et al., 2010; Drack et al.,2007; Keller, 2005; Letelier & Cornish-Bowden, 2011; Marcum, 2009; Newman, 2003; Powell & Dupré, 2009; Robert, 2007; Trewavas, 2006; Van de Vijver et al. 2009; Welch, 2009; Westerhoff & Palsson, 2004).

It had been argued that there is conceptual unclarity as to what a ”system” means in systems biology, and, as a corollary, that there may be several meanings of ”systems biology” and its ”holism” (see Definitions and Key concepts, as well as Gatherer, 2010; Keller, 2005; Marcum, 2009; O’Malley & Dupré, 2005).

Some papers focused on conceptual and methodological challenges (De Backer, 2010; Keller, 2005; O´Malley & Dupré, 2005). Publications had identified key conceptual developments, such as an increased focus on complexity, context, process, emergence and robustness, and as a methodological corollary on integration and accounting for the temporality of living organisms (Calvert & Fujimura, 2011; Keller, 2005; Marcum, 2009; O´Malley & Dupré, 2005; Powell & Dupré, 2009).

It had been pointed out that the theory of systems biology would likely become dominated by an engineering mindset, and scholars had highlighted differences between machines and the living, and raised questions as to how this may affect our view of the living world (Calvert & Fujimura, 2011; Fujimura, 2011; Keller, 2005; 2007). It had been noted that systems biology in large part represents a continuation rather than break with molecular biology and a new form of reductionism (Bothwell, 2006; Keller, 2005; Newman, 2003; O’Malley & Dupré, 2005). De Backer and collegues, for example, argued in 2010 (p. 40) that, ”SB’s ‘holism’ thus exists in making its research as systematic, interdisciplinary, large-scaled, and high-throughput as possible, with a view to answering how genotype, environment and phenotype are linked in terms of molecular interactions”. However, Marcum (2009) argued that, while many systems biologists may still be committed to reductionism, biology might be technologically driven towards a paradigm shift where reductionism and mechanism are replaced by a new holism in the form of an organicism, which emphasizes *downward causation* (see Definitions and Key concepts). Importantly, Marcum also pointed out that

systems biology may involve a middle ground of what he called ”emergent mechanism”, which pays greater attention to context than previous ”reductive mechanism”, but still renders emergent phenomena mechanistically explainable (Marcum, 2009, p. 51, see also Richardson & Stephan, 2007).

Joyner and Pedersen (2011) had asked whether systems biology represents anything fundamentally new from physiology, which also focuses on systems dynamics, and whether it could still be considered too cell-focused or molecular and in need of a broader view of social and environmental factors.

Theorists had also argued for new models, new mathematics and conceptual innovation in order for systems biology to model life (Keller, 2005; Omholt, 2002). In particular, the need to clarify and develop new ideas of self-organization, emergence, downward causation and inter-level causation in living systems had been pointed out (Keller, 2005; 2007; Khushf, 2008; O'Malley & Dupré, 2005; Powell & Dupré, 2009).

With direct relevance to systems medicine, Strand et al. (2004) had argued in an early paper that metaphors of complex systems theory (e.g. ”attractors”, see Definitions and Key concepts) cannot account for what they call “human complexity”. In another early paper, Khushf (2008) also argued that downward or circular causation, psychosocial dynamics and the interpretative nature of health and disease would always make clinical practice ”messier” than what an engineering ”circuit diagram metaphor” can account for.

After the start of this project Wolkehauer and Green (2013) also pointed out that, “In systems medicine, our understanding of cellular functions must be integrated across multiple levels of structural and functional organization: from cells to tissues and organs to whole organisms, and from cell functions (…) to the physiology of organs or the human body”. They argued for a shift in focus from molecular pathways towards multi-level organization, to counter reductionism in fledgling systems medicine, while also pointing out that conventional dynamic systems theory may not be up to the task. In her Phd, Green (who became my co-supervisor), pointed towards further research on systems medicine, for example the uncertainty as to what the promise of “quantifying wellness” and ”demystifying disease” may mean, the feasibility of developing whole digital patient models, the social implications of systems medicine, its clinical utility and cost-effectiveness (Green, 2014).

Gietzelt et al. (2016) reviewed methods used in systems medicine, identifying no methods specific for systems medicine, as opposed to systems biology and related fields.

Coming to my attention only after the research phase for the papers of this thesis, Döring et al. (2015) published a major sociological book on systems biology, examining many of its facets. Importantly, its findings underscore the need for theoretical clarification of its basic concepts (life, system, reductionism, holism, and model), pointing out especially that "the concept of holism in systems biology remains unspecific and requires clarification to better understand the epistemological assumptions inherent in systems biology" (Döring et al., 2015, p. 89).

2.5.2. Research on the overall utility of systems medicine

Considering the overall utility of systems biology, Joyner and Pedersen (2011) had pointed out lack of beneficial clinical strategies arising from "omics" technologies. In a short commentary, Burke and Trinidad (2011) had also raised questions about the predictive value, potential for overdiagnosis (see Definitions and Key concepts), false positives/negatives and iatrogenic harm arising from systems medicine specifically, as well as its potential to improve significant environmental factors and health behaviors.

After the advent of this project, Khoury et al (2012) noted that "The lack of information on the clinical utility for most proposed P4 applications produces an evidence dilemma and a conundrum for implementation into practice", calling for a population perspective to be added to the four Ps, involving an ecologic model of health, principles of population screening, evidence-based decision making, and public health.

In the last year of my research, Diamandis (2015) published the first article that explicitly pointed out problems of iatrogenic harm in P4 medicine. Drawing on experience in cancer screening and the discovery of indolent disease, he cautioned against overdiagnosis and overtreatment.

Important discussions about personalized medicine more generally (not specifically about systems medicine) had considered conceptual issues, methodological limitations, problems of genetization, depersonalization, ethical and legal issues such as informed consent, disclosure dilemmas, personal identity, data security, as well as the current discrepancy between

marketing and the utility of genomic risk profiling and personalized medicine (Bartol, 2013; Boenink, 2009; McEwen & Getz, 2013; Reydon et al., 2012, Rehman-Sutter & Müller, ed., 2009; Forgò et al., 2010; Joyner et al., 2016; Juengst et al., 2012; Ziegelstein, 2015). In particular, Tutton (2012, 2014) had shown how the concept of personalized medicine has come to be rearticulated in a technoscientific concept, and stands in tension with traditional, humanistic ideas of personalization. During the writing of this summary, I also became aware of a paper (in French) by Guchet (2014) arguing that personalized medicine involves a reconceptualization of the patient as ”actionable” pointing towards intensified responsibility of all citizens with regard to their own health (similar to my paper II).

2.5.3. Research on medicalization and systems medicine

Before the start of this project, in the context of considering the overall utility of P4SM, Newman (2003) and Potthast (2009) had pointed out that reductionism influences and potentially damages our view of human nature. But to my knowledge, few, if any, publications have to date explicitly addressed the question of medicalization in systems medicine.

2.5.4 Originality of the thesis

My scope in examining P4 medicine systems is in one sense more specific, and in another wider, than the research reviews above. It is more specific in that it studies systems medicine (which is seen as a cutting edge development representing and illuminating different trends) *in particular* (not the wider movements of personalized/precision medicine and digital health). It is wider in discussing its philosophy broadly and focusing on its overall clinical utility. It also involves an attempt to link all theoretical levels: Conception of person, health and disease to methods, to medicalization, to clinical utility in practice. This is done from the perspective of primary care medicine, which is where P4SM will be implemented.

I thus argue that this thesis presents the first comprehensive assessment of P4SM and its promises, from the perspective of clinical primary care medicine. When this project started, systems medicine was a little known concept in the making, and the research started at an

early time-point. It thus addresses imminent questions with high relevance for the future of primary care, based on a material that has not been gathered or examined comprehensively in light of the current questions and perspectives before. In particular, critically examining the material in light of the clinical and theoretical challenges of primary care medicine contributes to the originality of the thesis. It is at the intersection of the material and these perspectives that the originality arises.

AIMS AND RATIONALE

3. Aims

The overarching promise of P4 systems medicine (P4SM) is a revolution in clinical practice through a new form of holism.

The aim of this thesis is to critically analyze P4SM as a *proposed* theoretical framework for the future of primary care. By *framework* I here mean an ontology, philosophy of causation, epistemology and methods in research and practice (see Definitions). By *proposed* I mean something that is not yet realized, but a proposition about the future based on theoretical deliberations – a vision. It is also analyzed specifically as a suggested framework for primary care by holding its underlying theoretical deliberations and assumptions, proposed methods and promises up against a set of pressing challenges in primary care medicine.

One main focus is the meaning and implications of the *holism* proposed by P4SM, and the extent to which systems medicine can provide an *integrative* framework that can counteract fragmentation in medicine and ensure genuine, personal care. Another main focus is whether this holism, with its eventual limitations, can actually be predicted to lead to a revolution in the clinical utility of primary care medicine, especially preventive medicine.

More specifically, paper I (Vogt et al., 2014a) of this thesis was aimed at answering whether the holism or integrationism of P4SM could theoretically account for the *patient-as-a-person* and thus unite humanistic and scientific medicine. It focused specifically on works by systems biologist Denis Noble as compared to physician-philosopher, Eric Cassell.

Paper II (Vogt et al., 2016a) aimed to analyze the concept of holism in mainstream P4 systems medicine, both with regard to its methods and conceptualization of health and disease. It did so especially in light of the concept of medicalization, broadly understood, relying on the concepts of biohealth (Downing 2011), biomedicalization (Clarke et al. 2010) and biopolitics (Rose, 2007).

Paper III (Green & Vogt, 2016) picked up on the theme of medicalization and potential waste and harm as well as the history of preventive medicine. It aimed to examine the promises of overall clinical utility of P4SM´s new preventive strategies.

4. Rationale

"As accurate predictions of the future are essential to getting along, uncertainty is the great problem of life."

- Eric Cassell (2004)

Medicine is a pragmatic field. Here, I will elaborate the rationale for systematically examining something as intangible as theories, proposed visions, methods and promises in this context.

According to the WHO (2008), primary care medicine should be regarded as the cornerstone of future healthcare worldwide. To anticipate its future and promote its sound development would therefore be very beneficial.

As I have outlined above there is a striking "hand in glove" correspondence between the promises of P4SM all its appealing words (e.g. personalization, holism, patient-centeredness) and the challenges of primary care medicine. This may facilitate acceptance of P4SM as a framework for primary care medicine without substantial critical examination.[21] P4SM will likely affect primary care medicine in the coming years. However, one cannot assume that P4SM will turn out *as promised,* and the concept deserves scrutiny even on the biomedical drawing-board. The rationale for this thesis is simply for GPs to be on the train before it leaves the station, in fact, before it is put on the tracks. It is likely that systems medicine will have profound influence on research and practice in the coming years, and even now, in the form of a dream only, it shapes action in funding, research and even in the clinic. It may well have new consequences and implications beyond those of past biomedicine. So, to echo Bertalanffy in the opening quote of Chapter 1, "*we have to come to terms with it*".

[21] Take as examples publications by Ahn et al. (2006a;2006b) and a George Swift Lecture by Tony Kendrick, professor of primary care, where the novel promises of a P4SM are propagated without much criticism (Kendrick, 2012).

4.1 Scientific responsibility and quaternary prevention

As goals are important for our actions today, a general awareness of the goals of medicine underlies the rationale of this thesis. Medicine is driven by goals. Goals may be divided into *stated* and *unstated*. The Encyclopedia Britannica defines medicine by referring to its *stated goals* as "the practice concerned with the maintenance of health and the prevention, alleviation, or cure of disease" (Encyclopedia Britannica, 2016). This is medicine´s public face and source of positive self-understanding. However, medicine is also driven by *unstated goals*. Historian Harold Perkin writes about professions that,

> "They live by persuasion and propaganda, by claiming that their particular service is indispensable to the client or employer and to society and the state. By this means they hope to raise their status and through it their income, authority and psychic rewards (deference and self-respect)" (Perkin, 1989, p. 6).

A key characteristic of a profession is that it is based on expertise in a systematic body of knowledge. In order to generate a necessary level of trust, it needs to show that this theoretical body enables it to perform a useful and ethically justified service to society. However, the way medicine develops its theoretical basis, its visions and promises, might not only be influenced by its stated, but also its *unstated goals*. Crucially, medicine is to a considerable extent allowed to define its own *raison d´être*, that is, its conception of the human body, disease and health, as well as what aspects of life should be regarded as within medical jurisdiction and control (that is *medicalized*). A key element of medicalization is the definitional process itself, the process of defining an aspect of life in medical terms *as controllable*.

A crucial element of medical self-regulation and ethical practice should therefore be to conceptualize the human body in a way that does justice to its nature and to set boundaries for medicalization. The setting of boundaries for medical practice underlies the ancient medical maxim *primum non nocere* ("first do no harm") as well as contemporary efforts in *quaternary prevention* (efforts to prevent negative effects of medicalization, see Definitions and Key concepts) and *scientific responsibility* (Brodersen et al., 2014; Getz, 2006; Forssen et al., 2010; Jamoulle, 2015). A part of the rationale for this thesis is to contribute to such professional "boundary work" by focusing on persuasion, theorizing, promises and visions in P4SM. For better or for worse, professionals also exercise *power*, in individualized healthcare and population health, in politics and, most fundamentally, over our very view of ourselves.

4.2. Proactive study of scientific theories, visions and promises

> *"Whether doctors like it or not, human action is inevitably theory driven. We act as we do (we even see what we see) because we have a concept – a theory – about what will be the consequences of our actions"*
>
> - *Eric C*assell (2004)

As we are likely act according to the theories, promises and visions of P4SM, it is important to contribute to critical reflection and *anticipatory* and *proactivity* study of P4SM from the perspective of medical generalists. Although the "*before the fact*" acts of medical theorizing and construction of visions are generally not afforded the same critical scrutiny as empirical results that can be gathered "*after the fact*", they are significant.

To back this claim, one can only look at the fact that top scientists lay down much time and resources in constructing theoretical papers and roadmaps towards the future of medicine: This is because they are intended to guide the biomedical effort. In P4SM there is currently a philosophical discourse that is not primarily about what has already happened, and can now be evaluated quantitatively or scientifically, but about the conceptual foundation for future medicine (Boogerd et al. 2007, eds.; Noble, 2006). Given that the discourse *is* important, and that it is important *now*, one avenue for examining P4SM is *as it stands*, that is, as theoretical deliberations, visions, promises etc.

In sociology and science studies there is also a growing awareness of the importance of future visions in shaping practice. However, both medical and social sciences prefer evidence-based methods focused on "after the fact facts" and lack methods for studying the future, or visions thereof. Building on methods from foresight practices, future studies, technology assessment, and strategic planning, a number of scholars have therefore recently made what sociologist Cynthia Selin (2008) calls "creatures of the future tense" their object of study: biomedical promises, anticipation, visions, expectations etc. (Borup et al., 2006; Brown & Michael, 2003; Döring et al., 2015, Chapter 3; Hedgecoe, 2004; Tutton, 2012; 2014). Such projects aim "to study the future in order to make better choices in the present" (Selin, 2008, p. 1880). Although I have not closely followed the methods of these scholars, my rationale is in alignment with theirs.

4.3. Real-time, early health-technology assessment and "systems bioethics"

Relatedly, my project may be viewed as a form of health technology assessment (HTA).[22] Guston and Sarewitz's (2002) have developed the concept of *real-time technology assessment* (real-time TA), which has been pointed out as especially relevant for the study of emergent systems biology (Robert, 2007). Its central idea is that critical research should be integrated in natural science and engineering efforts from the outset in order to "provide an explicit mechanism for observing, critiquing, and influencing social values as they become embedded in innovations" (Guston & Sarewitz, 2002, p. 95).

Similarly to "real-time TA", "*early stage health technology assessment*" has been proposed as a strategy for research on future systems medicine, aiming at "rapid falsification" of strategies that "are unlikely to provide sufficient added value in real-world clinical settings or public health practice" (Steuten, 2016, p. 31). Again, although the current work does not follow these specific methods, *its rationale* is congruent with that of *real-time* or *early stage* health technology assessment.

Finally, although I have not considered this a bioethics project in a narrow sense, it does have an ethical component. Theories, promises and visions guide action and are therefore ethically important. Philosopher Jason Scott Robert states bioethics should move towards a "systems bioethics" in the wake of the Human Genome Project and with the rise of systems biology.

> "Just as biologists are now moving toward a more integrative systems biology, perhaps so too should bioethicists move toward a more integrative 'systems bioethics'. Research in systems bioethics would be (…) integrated with studies in the history and philosophy of biology and social and political studies of science and technology, and employing a variety of methods from the humanities and social sciences (…). This would then serve as a basis for proactive deliberation about scientific, ethical, and political issues together and interactively" (Robert, 2007, p. 369).

The above statement is also congruent with my rationale.

[22] Technology assessment is a wide category "encompassing an array of policy analytic, economic, ethical, and other social science research that attempts to anticipate how research and research-based technologies will interact with social systems" (Guston & Sarewitz, 2002, p. 95).

METHODS AND MATERIAL

To examine a *proposed* future framework for future medicine is not something the medical discipline provides a methodological framework for. It has no preconceived, repeatable operationalization. I have had to search out and draw on a disparate set of methodological tools and theoretical perspectives.

5. Methods

Method is at the heart of any academic project (Andersen & Hepburn, 2015). This thesis presents a critical historical-philosophical analysis of a material outlining P4 systems medicine as a future ”holistic” and ”personalized” theoretical framework for primary care medicine. It is methodologically situated in academic primary care medicine and the medical humanities.

Academic primary care medicine aims to provide theory and knowledge for general practice. Its most ambitious projects typically examine general, complex and multi-faceted problems and pragmatically draws on methods from a range of disciplines (Greenhalgh, 2007; Westin, 1986).

The medical humanities may be understood simply as the humanities (or Arts) applied to medicine. Its *raison d'être* is problems that cannot be adequately addressed and resolved by the methods of the natural sciences, such as accounting for the history, agency, experience, meaning and values of humans (Cole et al., 2014, p. 3). Rather than focusing on mathematical proof, experimental inquiry, mechanistic explanation and prediction (scientific ways of knowing), the humanities are directed at meaning and interpretation, or ”the disciplined development of insight, perspective, critical understanding, discernment, and creativity” (Cole et al., 2014, p. 3). The medical humanities also use methods from various disciplines such as history and philosophy. They promote critical thinking, explore conceptual issues in medicine and seeks to contextualize medical practice by studying change over time (Cole et al., 2014).

Application of methods from the humanities is often regarded as unreliable and thus "soft" or inferior in medicine. Some scholars argue that implementation of technologies and scientific innovation in complex systems should be evaluated using the same methods as for example new drugs (Catwell & Sheikh, 2009). However, my aim is not amenable to a traditional scientific or quantitative methodology. The reason is that my aim and research questions require an analysis of the theoretical assumptions and meaning that underlies the proposals and visions of P4SM as a future framework. Taking the perspective of a medical doctor situated in primary care medicine, I therefore adopt methods and perspectives at the crossroads of medicine, philosophy, history and social science. Such an integrative approach is both original and challenging.

In the following I will go into more concrete methodological details.

5.1 Philosophy of science in practice (PSP)

I have come to see a recent development in philosophy of science as particularly relevant for situating this thesis methodologically. This is *philosophy of science in practice (PSP)*.

What is PSP? Traditional analytic philosophy of science (as opposed to Continental philosophy) has mostly been focused on the logical or propositional relation between different theories and the world, neglecting the way science is actually performed and the role philosophy plays in this practice. Social studies of science and medicine on the other hand, have tended to focus on their practice, but have sometimes gone as far as to see the world as a social construction. As a corollary, philosophical understanding of medicine has been riven between an analytical and strictly naturalist understanding of disease and health and social-constructionism and normativism (Murphy, 2008). PSP attempts to offer a middle ground or synthesis, "an analytical framework that takes into consideration theory, practice and the world simultaneously (…) a conscious and organized program of detailed and systematic study of scientific practice that does not dispense with concerns about truth and rationality" (SPSP, 2006). It emphasizes, "a productive interaction between philosophical reasoning and a study of actual scientific practices, past and present" (Ibidem). Among the issues covered within PSP are the goals and philosophical assumptions of scientific developments in the making (Green, 2014, chapter 1).

Importantly, PSP is concerned not only with acquisition and validation of knowledge, but also how knowledge itself is shaped by its utility. It emphasis how ”human artifacts, such as conceptual models and laboratory instruments, mediate between theories and the world”, seeking to ”elucidate the role that these artifacts play in the shaping of scientific practice” (SPSP, 2006). In short, it is a form of philosophy of science that tends to analyze science ”as it is” in practice, rather than ”as it should be”, and that tries to account for the ”messiness” of scientific practice, just as academic general practice seeks to account for the ”messiness” of medical practice (Green, 2014, p. 6). In so doing it also aims to build bridges to other fields (Green, 2014, chapter 1; SPSP, 2006).

The case of systems medicine, its creation of a new theoretical framework, visions and promises for primary care medicine, may itself be seen as a form of *practice*, and due to its pragmatic outlook, its models of persons, health and disease are shaped not only for validity but also for their utility (see Definitions and key concepts).

The most important contribution of philosophy is perhaps the identification and critical analysis of hidden assumptions that underlie our actions, that are often taken for granted. A key endeavor here is *conceptual analysis*, that is, ”using various disciplines, but primarily philosophy, to define and to clarify ideas, terms, and issues related to medicine” (Cole et al., 2014, p 14). As my thesis combines conceptual analysis, evaluation of evidence, reflections of social implications and ethical considerations, it seems to fit well within philosophy of science in practice.

5.2 Critical thinking

This thesis is a *critical* analysis, or, as historian Peter Tosh simply puts it, ”The application of critical method to the primary sources” (Tosh, 2015, p. 122). My most important methodological tool here is critical thinking, which I take to have two related meanings.[23]

Firstly, critical thinking is a method for examining the logical *argument* itself (logos), as opposed to other aspects of rhetoric, which also traditionally involves ethos (the credibility of the one making the argument) and pathos (the appeal to emotions). A (logical) argument may

[23] The word *Kritike* originally meant ”a lifting and separating of an object in order to examine its properties” (Fuenmayor, 1990, p. 526).

be defined as an ”attempt to persuade by giving good reasons” (Bowell & Kemp, 2015, p. 4).[24] Critical thinking is about how to recognize, reconstruct and analyze an argument, how to separate it from other ”foul” acts of persuasion, and how to make a valid argument oneself: ”Successful critical thinking enables us to ensure that we have good reasons to believe or do that which people attempt to persuade us to do or believe, and helps to prevent us from doing and believing wrong or silly things” (Bowell & Kemp, 2015, p. 23).

The theories and visions of P4SM involve arguments – acts of persuasion. My primary material may be seen as containing one whole argument for P4SM, which I then proceed to analyze. Based on my philosophical and historical analysis, I myself then make arguments about P4SM that should be valid and sound. This means, for example, that I should avoid fallacies, straw man argumentation, obscuring *linguistic phenomena* (e.g. uses of language introducing ambiguity, vagueness and rhetorical questions in the argument) as well as *rhetorical ploys* (attempts to persuade without giving good reasons, including the use of buzzwords and jargon). In this thesis I employ critical thinking to reveal (in)consistencies, problems and gaps in the argumentation for P4SM as a framework for primary care medicine. However, instead of providing more detail on it here, I will refer the reader to Bowell & Kemp (2015) for an authoritative presentation, and admonish him/her to scrutinize whether my critical thinking has been sound.

Secondly, I also take the concept of ”critical thinking” to have a somewhat wider meaning. This is found in the philosophical tradition of ”critical theory”, and fields employing it, for example ”critical psychology” (Fuenmayor, 1990; Greenhalgh & Russell, 2010; Madsen & Grennes, 2012). In a broad sense, any philosophical approach directed at exposing specific circumstances that may disempower human beings could be called ”critical theory” (Bohman, 2005). Critical thinking focuses on assumptions that are concealed in our usual ways of acting and thinking (Madsen & Grennes, 2012). Its purpose is not destructive, but may rather be seen as a form of quality control that ultimately can lead to a more adequate and responsible practice. This thesis directs such a critical perspective towards P4SM, and is an example of what could perhaps be called ”critical medical thinking”. In the same way

[24] Bowell & Kemp (2007, p. 10) more formally define an argument as ”A set of propositions of which one is a conclusion and the remainder are premises, intended as support for the conclusion,” where a proposition is defined as ”The factual content expressed by a declarative sentence on a particular occasion”. The same proposition may be expressed by different sentences, (and) the same sentence can express different propositions depending on context (e.g. who utters it).

as ”psychologization” is a main focus of critical psychology (Madsen & Grennes, 2012), a focus on medicalization or *overmedicalization* (i.e. medical control of human life with potential disempowering side-effects) would be a key example of such thinking in medicine.

5.3 History

Another important element of my thesis is a historical reconstruction and analysis of events (e.g. conceptual developments) in biomedicine that have happened in our immediate history (especially the last 15 years) and that have partly unfolded as I have performed the research. In this research my questions have thus in part been answered through the methods of History. As is proper in historical science (Duffin, 2010), I have divided my material in primary and secondary sources (see Material section below), which I then *read*, *analyze* and *interpret* to provide *evidence* and *arguments*. According to the historical method (source criticism), sources are critically examined in order to establish their *validity*, and interpreted in order to understand their *meaning*.

5.4 Social sciences

Although I do not identify my work strongly with sociological methods, I lean on my background in the history of professions and the welfare state (see Preface) (see e.g. Perkin, 1989). Such social history is overlapping both with sociology and political science (see e.g. Perkin, 1989). In particular, I employ sociological perspectives on medicalization and studies of science visions (Borup et al., 2006; Clarke et al., 2010; Rose, 2007; Selin, 2008; Tutton, 2012; 2014).

6. Material

6.1 Collection of material

This project is based on a five-year long, extensive research into P4SM. This is not a subject that has been easy to delimit. The intention has not been to find *every* relevant source, but a material that is comprehensive enough and *representative* in describing P4SM as a proposed, emerging framework for primary care medicine. I have mainly focused on written sources, primarily scientific journal articles (mostly reviews, perspective articles, opinion articles and editorials), but also other online publications, roadmaps, books and webpages. I have also attended conferences on systems medicine. Much of my material did not exist when the project started and I have thereby studied a development in the making, a ”moving target” (see figure 2, section 1).

The complexity and breadth of my subject does not allow for systematic literature searches as the only means of finding and delineating a suitable material. Such an algorithmic approach is too inflexible in identifying the relevant sources, which itself involves acts of interpretation, and is only one step on the way. For example, in order to evaluate the mainstream thrust of P4SM, I have had to identify and focus on what I came to identify as the most prominent agents and thought leaders (e.g. Leroy Hood and Denis Noble).

In my research I have still employed some searches using the PubMed database. I have done so in order to satisfy, as far as possible, the demands for reproducibility of the research process in academic medicine, a demand that is not shared in the same way by philosophy or journals of history and philosophy of medicine. As the PubMed (Medline) search engine encompasses most publications within biomedicine, I assume that most of the relevant publications, especially written primary sources from journals on P4SM (which is a biomedical development), are available here. As a large proportion of articles relevant to medicine are indexed in PubMed, I also assume that most relevant secondary sources are available here, although I realize that some articles from the social sciences and humanities are not.

Although I researched and read important sources during 2011, the more systematic part of my research can be said to start with a PubMed search on ”("systems biology" OR "systems medicine") AND (philosophy or theoretical)” on 2012-03-12. This search was performed last

2015-08-26 and aimed at identifying a broad material, which could serve as a point of departure. At the start of the project there were few publications referring specifically to ”systems medicine” and ”P4 medicine”. The second crucial PubMed search I performed was plainly ”systems medicine”, on 2014-01-30. The purpose was to capture *all* publications on this specific concept. In February 2014 I performed a number of searches on what I perceived to be key thought leaders or visionaries in systems biology and medicine, including Denis Noble and Leroy Hood, examining articles back until 2001. In order to acquire an appropriate material for paper II, I performed a third crucial search: (“systems medicine” OR “P4 medicine” OR “4P medicine”). This search was repeated 2016-02-11 during research for the revision of paper III, a date which may mark the end of my active search for publications.

Apart from these searches, I have pursued my aim through ”snowballing”, e.g. by searching references for references, a number of Google searches, searching publication lists of key research institutions, receiving references from colleagues and coauthors, discovering sources through social media (I have followed key figures and institutions on Twitter and Facebook). I have made use of the Amazon.com engine to search for books on key authors and systems medicine and biology. I have also interviewed one prominent systems biologist (Stig Omholt, personal communication, 2012) and attended two conferences on systems medicine where a number of its prominent opinion leaders or visionaries attended[25]: Firstly, the “Pioneers of health and wellness” in Lyon, 2014, and secondly, the “1st International Conference on Systems and Complexity in Health”, Washington, 2014. I have also attended a workshop (“Winter School”) on “Integration and Translation in Systems Medicine” at the Research Centre for Biotechnology, Society and the Environment in Hamburg.

6.2 Selection and systematization of material

In my collection of material, I have continually made choices about what I regard as significant to the aim and research questions and thus what to select. I have followed a hermeneutic approach, identifying and categorizing the relevant aspects of P4SM as I go along, and focusing on material that I *interpret* as especially relevant for my aim, both with regard to primary literature and secondary literature (see below). The first stage in selecting material is to select what to collect and what to exclude when performing PubMed searches

[25] Among the attendees were Leroy Hood, Charles Auffray and Howard Federoff.

and other searches (e.g. Google, websites, reference lists). I then proceeded to systematize the material in different categories, arranging them in different folders (more about the process of reading and categorizing below). Storing the material as pdf documents on my computer renders most of it searchable, something I have found very useful in my analysis, for example in identifying publications mentioning key words such as "downward causation" or "medicalization".

Primary material: I define my primary material as publications produced by advocates and visionaries of P4SM that outline it as a framework for the future of medicine, including primary care medicine. These are the publications that define my research subject (Duffin, 2010). At the end of this research, my primary material counted 320 publications, including journal articles, webpages, online publications and plenary speeches published online. The first source is from 2001, which is the year to which I limited my searches on key figures in systems biology. The year was chosen as representing the end of the Human Genome Project, which is when modern systems biology can be said to start. This material consists of both publications explicitly mentioning systems medicine and/or P4 medicine, but also publications on systems biology that are especially relevant to medicine. Additionally, I have categorized five books as belonging to my primary material (Boogerd et al., 2007 eds; Noble, 2006; Noble et al., 2012; Tretter et al., 2010; Walhout et al., 2013), making the complete number of sources in my primary material 325. This number is presented only to give an impression of the extent of the research undertaken (along with the number of sources in my secondary material, which is considerably higher). I do not pretend that this material is objectively delineated or complete, but I do claim that it is representative and comprehensive.

Importantly, I have not read every reference in this material thoroughly. Again, I follow an interpretative, hermeneutic approach. Based on a primary evaluation of the given material (e.g. title, abstract, keywords, authors, main conclusions), I further read those publications I interpreted as most relevant, sometimes several times. Others I have only scanned for content or read the abstracts. Throughout my research I have had to undertake a gradual reading, systematization and learning process, constantly assessing the literature in order to find the most relevant references. I have then been able to select from this broader primary material the sources that I have based the papers in this thesis upon. I have not been able to include all the references I have researched in the papers (the journals do not allow reference lists that long). In the narrowest sense, my primary material can be seen as those publications listed in

my papers, but they have been selected from a material that is much broader and that has been carefully studied.

I have especially focused on publications relevant to understanding P4SM as an envisioned framework *for primary care,* in accordance with my aim. That means that I have focused less on publications that pertain to hospital-based subspecialities (e.g. hepatology, neurology, critical care medicine, infection). I have focused on finding and selecting publications that are conceptually oriented and directed at describing philosophy of personhood, health and disease and approaches to clinical medicine.

In my research and selection of material I have emphasized publications by a number of key visionaries and thought leaders, whom I have come to recognize during my research. In paper I, I have emphasized Denis Noble (who collaborates closely with e.g. Peter Kohl, Peter Hunter, Stig Omholt, and others associated with the Physiome and Virtual Physiological Human projects). In paper II, I focus on Leroy Hood (who collaborates closely with for example Charles Auffray, Nathan Price, Rudi Balling, Sui Huang and Stuart Kauffman, and who is associated with the Hundred Person Wellness Project (100 K Wellness Project).

I have identified Leroy Hood as *the* main visionary and thought leader of P4SM. Hood, who is also a member of the American Philosophical Society and the American Association of Arts and Sciences, has influenced the development of personalized medicine since the 1990s (Kevles & Hood, 1992) and is widely regarded as one of the most influential visionaires in biotechnology (Hariri & Gallagher, 2015).

The delineation of the material has been challenging, as systems biology and medicine are not monolithic or clearly defined fields. It would for example be tempting to take all sources that do not mention ”systems medicine” or ”P4 medicine” explicitly and exclude them from the my material, but the reality is that it is impossible to clearly separate systems medicine from systems biology. If one demarcated the material in this way, the papers of Denis Noble would, as an example, be excluded – he does not use the term ”systems medicine” or ”P4 medicine” explicitly although his publications are clearly written with medicine in mind. Publications before 2004 do not mention systems medicine, but the combination of systems biology and medicine is apparent from 2001 (Ideker et al., 2001, Hood, 2002; see also Hunter et al., 2002; Kitano, 2002a; 2002b; Noble, 2002). Essentially, what these publications propose is systems medicine, and it would be wrong to exclude them completely, although later publications give

a more up to date and comprehensive and view of the concept (e.g. Alyass et al., 2015; Antony et al., 2012; Benson, 2016; Boissel et al., 2015; Duffy, 2016; Hood et al., 2015; Sagner et al., 2016; Wolkenhauer et al., 2014).

It is also hard to separate P4SM from genomics, other ”omics”, from personalized (or precision) medicine in general or from big data medicine, *in silico* medicine and digital health. P4SM is influenced by and overlap with all of these, but the field is also somewhat more constrained (see my Overview and Background). I have therefore made it a requirement in selecting the material that the authors call what they do systems biology or medicine or that they perform their modeling guided by some *theoretical idea of systems* (not only bioinformatics or machine learning for example). I see this as setting systems biology apart for other in silico or big data biology. These are the reasons why, for example, I consider Google´s Baseline Project in computational medicine as falling *outside* my primary material.

Notably, one book (Schmitz & Wolkenhauer, 2016), the first to be explicitly focused on systems medicine, was published in early 2016. This was after I had finished my research and submitted paper III, so the book became known to me too late to be included in my primary material. Due to lack of time and practical limitations I have not been able to systematically research the literature that have become known to me after my last literature searches in early 2016.

Finally, concerning my primary material it should also be noted that I have an extensive material concerning topics that are neither secondary material nor background material, nor on systems medicine. This concerns publications coming from within biomedicine on themes that overlap with systems medicine, such as personalized medicine (alternatively precision or stratified medicine) more generally, various strategy documents and political visions for the future of healthcare, synthetic biology, eHealth, mHealth, “quantified self” and artificial intelligence is medicine. These publications may be seen as visionary papers on a broader movement in biomedicine of which systems medicine forms a nexus, a cutting edge part. They are hard to place in my material, but it is most stringent to see them as a less systematical and rigorously gathered part of my primary material than the core part of my material on systems medicine more specifically. Examples would be Eric Topol´s book “*The Creative Destruction of Medicine”* (2012), President Obama´s Precision medicine initiative (NIH, 2015) and early publications on personalized medicine (e.g. Kevles & Hood, 1992).

Secondary material. I define my secondary material as that produced by other authors (mainly non-systems biologists) on the same or similar subjects as mine (Duffin, 2010). Together with what I will call my background material (see below), my secondary material is an absolutely crucial tool to my analysis. It can be divided in different categories:

- *References written on systems biology, but without explicit mention of the concept of systems medicine. These have been important for understanding and evaluating the philosophical basis of systems medicine.*[26]
- *References written specifically on systems medicine* or *P4 medicine*.[27]
- *References written on personalized medicine (precision or stratified medicine), genomic or molecular medicine, but without specific reference to systems biology or medicine.*[28]
- *References written on developments that are related to and overlapping with, but not specifically directed at P4SM.*[29]
- *Refererences not written on systems biology or medicine, but on topics in the philosophy of biology that, are still especially relevant when considering my subject.*[30]

[26] Examples of this category include Boogerd et al., 2007; Bothwell, 2006; Calvert & Fujimura, 2011; De Backer et al., 2010; Döring et al., 2015; Drack et al., 2007; Fujimura, 2011; Gatherer, 2010; Green, 2014; Wolkenhauer & Green, 2013; Keller, 2005; 2007; Letelier & Cornish-Bowden, 2011; Marcum, 2009; Newman, 2003; O'Malley & Dupré, 2005; Potthast, 2009; Powell & Dupré, 2009; Robert, 2007; Trewavas, 2006; Van de Vijver, 2009; Welch, 2009; Westerhoff & Palsson, 2004.

[27] Examples of this category include Burke & Trinidad, 2011; Diamandis, 2015; Gietzelt et al., 2016; Joyner & Pedersen, 2011; Khoury et al., 2012; Khushf, 2008; Strand et al., 2004; Wolkenhauer & Green, 2013.

[28] This part of the material includes conceptualization of persons, health and disease in genomic personalized medicine and molecular biology (e.g. Boenink, 2009; Genuis, 2008; Guchet, 2014; Juengst et al., 2012; McEwen & Getz, 2013; Tutton 2012). It includes references on the history of the human genome project and personalized medicine thereafter, especially the problems of biocomplexity encountered and promises not kept, including concepts such as missing heritability, genetic heterogeneity and problems with the common disease common variant hypothesis (e.g. Caspi et al., 2006; Check Hayden, 2010; Geddes, 2014; Fox Keller, 2014; Hall, 2010; Kaiser, 2012; Maher, 2008; Turkheimer, 2011; Wright & Hastie, 2001; Zuk, 2012). The latter category includes references concerning successes and limitations with risk prediction and prevention in gene-centric personalized medicine (e.g. McPherson & Tybjaerg-Hansen, 2016; Noble et al., 2014; Thanasoullis & Vasan, 2010). Moreover, this secondary material includes a wide range of references on issues of medicalization in personalized medicine as well as its overall utility (benefits vs waste and harm) (e.g. Bloss et al., 2011; Boccia et al., 2014; Brunham & Hayden, 2012; Callahan, 2011; Cassiman, 2011; Caufield, 2015; Cooper, 2015; Heshka et al., 2008; Jameson & Longo, 2015; Joyner & Prendergast, 2014; Joyner & Paneth, 2015; Mardis, 2010; McGuire, 2007; McGuire et al., 2013; Nebert & Zhang, 2012; Nordgreen, 2014; Ransohoff & Khoury, 2010; Roberts & Ostergren, 2013; Sørensen, 2016; Welch & Burke, 2015). The latter also includes references on communicating risk and ability to change health behavior in personalized medicine (Bloss et al., 2011; Bloss et al., 2016; Comstock, 2016; Grant et al., 2013; Hollands et al., 2016).

[29] Examples of this category are references on epigenetics (Lock, 2013; Nicolosi & Ruivenkamp, 2012; Niewöhner, 2011; Smith, 2011), omics and big data medicine (Ioannidis, 2016; Leonelli, 2014; Livingstone, 2015), the quantified self movement and participatory medicine (Aasarod 2012; 2014; Kappelgaard, 2015; Knoblauch, 2014; Linster, 2011; Prainsack, 2014) and digital health, mHealth and eHealth or *in silico medicine* (Tjora, 2004; Lupton 2012; 2014). Here medical doctor Robert Wachter has written an important, rare early work from a medical point of view (Wachter, 2015).

[30] This material includes references on complexity, systems theory and mathematical modeling in biology and the need for biological theory for tackling complex systems (e.g. Bateson, 2005; Bertalanffy, 1969; Deacon, 2012; Drack et al., 2007; Gare, 2013; Gilbert & Sarkar, 2000; Hooker, 2013; Kauffman, 2008a; 2008b;

It is important to note that the division between primary and secondary literature is not always strict and that the same reference may play both roles (Duffin, 2010). In this thesis, a number of references included in the primary material that are written by systems biologists are so self-reflexive that they have also functioned as secondary material. Examples are (Bruggeman & Westerhoff, 2007; Buchman, 2002, Boogerd et al., 2007 eds; Mesarovic & Sreenath, 2005; Noble 2010; Rosslenbroich, 2011; 2016).

Background material: In addition to my primary and secondary material on systems medicine I want to describe what can be called a background material. This material is absolutely central to the method of this thesis as it functions as a lens through which I analyze my subject. This forms the basis of much of my description in the Background chapter and describes other theory that is central to the analysis. This is also the material on which I have based my description of the challenges of primary care, against which I evaluate the promises of P4 systems medicine.

In paper I, my coauthors and I relied especially on background literature by Eric Cassell as a lens through which I viewed and compared the philosophy of Denis Noble (Cassell, 2004; Cassell, 2010; Cassell, 2013).

In paper II, we relied especially on background literature concerning philosophy of medicine, holism and humanistic medicine (e.g. Boenink, 2009; Engel, 1977; Gadamer, 1996; Hofmann, 2002; Marcum, 2008; McWhinney & Freeman, 2009; Miles & Mezzich, 2013), "the medicalization of health and life itself" (e.g. Armstrong, 1995; Callahan, 1998; Clarke et al., 2010; Downing, 2011; Meador, 1994; Rose, 2007).

In paper III, Sara Green and I relied on literature on the history of and challenges with the utility (balance of benefits and harms/costs) in disease prevention in primary care medicine (e.g. 4S Study Group, 1994; Ashenden et al., 1997; Austin et al., 2013; Biller-Andorno, 2014; BMJ; Bodenheimer, 2005; Boyd et al., 2005; Brodersen et al., 2014; Cooper, 2015; Dybczak & Przywara, 2010; Echt et al., 1991; Getz, 2006; Getz et al., 2005; Gøtzsche & Jørgensen,

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Lewkowicz, 2011; Mazzocchi, 2008; Mikulecky, 2001; Moreno et al., 2011; Rose, 1997; Rosen, 1991; Ruiz-Mirazo et al., 2010; Thompson, 2007; Woese, 2004), concepts that are central to systems biology and medicine, especially materialism/physicalism (Stoljar, 2009), information (Darden & Tabery, 2009), process (Bickard, 2011; Coffman, 2011), mechanisms (Darden, 2008), reductionism (Brigandt, 2012), self-organization, emergence (Van Gulick, 2001) and especially downward causation (Carroll, 2011; Emmeche et al., 2000; Juarrero, 1999; Soto et al., 2008; and special issue in Interface Focus, see Ellis et al., 2012) as well as unpredictability of complex systems (Bishop, 2011; Cilliers, 2011; Kauffman, 2008a).

2013; Hofmann, 2015; Hetlevik, 1999; Jørgensen et al., 2014; Krogsbøll et al., 2012; Løberg et al., 2015; Look Ahead Group, 2013; Parekh & Barton, 2010; Petursson et al., 2009a; 2009b; 2012; Puliti et al., 2012; Skolbekken, 1995; Starfield et al., 2008; van Staa, 2014; Welch et al., 2011; Welsh, 2014; Yudkin & Montori, 2014), the complexity and mind-body relations of the human organism (Beauregard, 2007; Danese & McEwen, 2012; Dubos, 1959; Eisenberger & Cole, 2012; Engel, 1997; Fretheim, 2007; Holt-Lunstad et al., 2010; Kendler, 2005; Marmot, 2005; Novack et al., 2007; Pavlov & Tracey, 2015; Shonkoff et al., 2009; Stange, 2009a), as well as literature on medicalization (previously described).

6.3 Research, reading and analysis of the material

My analytical method in this research project is a historical-philosophical analysis of the theories, visions and promises of systems medicine, as described by my primary material through the lens of my Background material and with reference to my secondary material.

My analysis is based on an extensive reading of both primary, secondary and background material. However, much of the analytical work has not consisted in reading the different types of material, but in relating them to each other in an original way that produces an analysis *for primary care medicine*. I started out knowing virtually nothing about systems biology and systems medicine. I have then examined, analyzed and interpreted individual publications – and parts of individual publications – in light of my own theoretical understanding and theory, continually updating my understanding of what systems medicine is as a whole and how it may function as a framework for primary care. This continual, iterative and interpretative research process that can best be described by reference to the hermeneutic circle in which, "Human understanding is achieved by iterating between the different parts of a phenomenon and the whole that they form" (Greenhalgh & Russell, 2010). In this process, not only reading has been important. The writing process itself has been an important part of the analytical work. As Duffin (2010) points out, only in writing does the analysis and argument take a stringent form.

In line with the tenets of the humanities, I acknowledge my role as participant in this project of analysis and interpretation of data gathered, not pretending to have a fully objective perspective. Instead I have sought self-reflexivity as to my own background, interests and

intellectual biases in reading, selecting and interpreting the material, and I have tried to correct for them as far as possible (Duffin, 2010; Greenhalgh & Russell, 2010). Particularly, I have been aware of the position of my own research environment and the biases of belonging to a profession and subprofession (cf. “unstated goals” of medicine in section 4.1). At the same time I have been aware of the upsides of being a medically trained professional in evaluating P4SM, especially in knowing what is relevant for primary care medicine.

RESULTS, DISCUSSION AND IMPLICATIONS

7. Results

I will now present a summary of the results of the thesis, where I unify elements from all papers into one argument.[31] I will structure this presentation according to the previously described challenges of primary care medicine and corresponding promises of P4 systems medicine (P4SM) (see Background, sections 2.2 and 2.4).

- In **Section 7.1** I will present my results on the extent to which P4SM might counteract the challenge of fragmentation through its promised holism or integrationism. To what extent can P4SM offer a holistic form of personalized medicine conceptually and methodologically? To what extent can it connect "bio" to "psychosocial"? This section refers to findings in both paper I and II.
- In **Section 7.2** I relate how this new technoscientific holism may in theory and practice entails a "holistic medicalization" of health and life itself. This section refers primarily to paper II, but also paper III.
- In **Section 7.3** I present my findings on what this above described technoscientific holism and holistic medicalization may mean for the overall utility (i.e. the balance benefits vs. harms/costs in the widest sense) of primary care medicine, especially with regard to preventive medicine. This section corresponds to paper III, but also paper II.

As my results have already been presented in the respective papers, I will here concentrate on the main elements of the argument. I will then proceed to deepen, elaborate, provide a broader perspective on, as well as point at implications of, this argument in the Discussion chapter. The key results I will present here are as follows:

- P4SM redefines the meaning of holism in medicine, constituting a "technoscientific holism".

[31] According to Holen's (2013) description of how the result section in a Phd thesis should be structured, this can be done in two ways. Either one can present each paper one by one (the most common), or one can present a unified summary of the results based on the aims of the study and thematically, point by point (quote Holen,"the most elegant").

- This technoscientific holism may contribute significantly counteracting fragmentation and understanding whole persons in medical practice. In particular, Denis Noble´s concepts of biological relativity and downward causation may prove fruitful.
- As a main downside, the technoscientific holism cannot be expected to become truly holistic, personalized or humanistic as in accounting for all aspects of human biocomplexity, notably "psychosocial" factors. It may be no more holistic than its computational and mathematical models, which are largely taken from physics, engineering and computer science and that render the body mechanistically explainable, calculable, predictable and controllable.
- At the same time P4SM, as proposed, entails an unprecedented "holistic medicalization" and will likely define the limits of future medicalization.
- Holistic medicalization comes with risks that its visionaries have not judiciously considered.
- There is a discrepancy between the far-reaching promises of a revolution in clinical utility through a novel form of holistic, personalized medicine and the real world complexity, unpredictability and uncontrollability of human biology.

7.1. The technoscientific holism of P4 systems medicine

7.1.1. General features of technoscientific holism

A main, overarching finding of this thesis is that, with P4SM the very idea of holism in medicine is redefined (see paper II). While holism has previously been associated with humanistic medicine (see Background, section 2.3), it is now adopted by personalized biomedicine and given a novel technoscientific meaning. Where does this leave primary care medicine? I will begin with results associated with some general features of this technoscientific holism.

One way to start is by asking what personalization means in P4SM. As in previous genomic personalized medicine it is about counteracting the universalism of medicine. However, in P4SM this counteracting of "one-size-fits-all medicine" becomes tied to the endeavor of holism, integration and counteracting fragmentation.

On a methodological level, new technologies now enable systems medicine to monitor each person as a system over time on multiple levels. One methodological consequence of this technology is the idea that a next step in personalized medicine should be a form of *n-of-1 studies*, where each person serves as his/her own control (see paper II, Hood et al., 2015; Hood & Price 2014a; 2014b; Li-Pook-Than & Snyder, 2013). However, it is early days for such studies, and the main strategy for counteracting universalism in P4SM is still *stratification*. As explained in the Background, this population-based strategy was key to personalization in genomic personalized medicine. What is new about stratification in P4SM is that while stratification in genomic medicine was based on DNA, stratification in P4SM is to be based on information pertaining to *whole systems* as defined by the utilized technology (see e.g. Duffy, 2016). It is primarily this strategy that is promised to lead to more accurate diagnostics, better risk predictions by determining risk in different strata ("risk stratification"), as well as more precise and effective preventive measures by developing treatments specifically targeted at each small group (Bjørnson et al., 2016; Flores et al., 2013; MacArthur et al., 2013; Wang, 2015).

A central, driving force behind the purported holism of P4SM is technological and scientific innovation. As explained in Paper II, I find that the words "holistic" and "integrative" are used in three different ways in my primary material:

1) Holistic measurements: Biology is now able to perform a range of detailed measurements at a scale, speed and cost that was previously impossible. Firstly, it can sequence genomes, which form the bedrock of systems medicine data, but secondarily it is now also able to perform more or less comprehensive measurements of a wide range of bodily factors on multiple levels over time, gathering longitudinal sets of *big data* on *each person*. These data are to a large extent still molecular "omics" data (multi-level only in the sense of genome, transcriptome, proteome and metabolome being seen as different levels), but technologies are also increasingly allowing attempts to measure the whole phenotype (or *phenome*) on cellular, organ and organism levels, and the so-called "exposome", that is environmental exposures (see Definitions and Key concepts for "omics", "phenome", "phenotype" and "exposome").

2) Holistic or integrative modeling: Holism or integrationism comes to mean the integration of the "holistic data" in computational or mathematical models of dynamic integrated

biological systems in order to make sense of the data and make predictions. This is the defining methodological element for P4SM and its holism (see primarily paper II).

3) Holistic theory and philosophy: The ”holistic” or ”integrative modeling” of ”holistic data” in systems medicine is guided by different forms of theory of wholes or *systems theory*. To a large extent this theory is defined by, or inherent in, the mathematical models that systems biologists employ to make sense of the data. These models, which are taken from mathematics, physics, computer science and engineering, become defining to the holism of P4SM, making it technoscientific. However, systems biology also involves development of other and more general biological philosophy apart from what is ”built into” the computational models themselves.

Very generally, the technological, scientific and philosophical developments that make up P4SM now allow the human organism to be conceptualized as a dynamic, integrated complex network or *system of systems* (see Paper II). I have no illusion that systems medicine is generally whole organism-focused today. Systems biology and systems medicine begin with a main focus on molecular and cellular wholes, but in the end, they conceptually aim towards understanding the whole body *as a system*, as a whole, dynamic process. While the thinking of most systems biologists may not entail a complete break with previous molecular and cell biology (see e.g. De Backer et al., 2010), systems medicine seems at least to a larger *degree* than previous biomedicine to acknowledge the complexity of the human organism and the importance of the interactions of all elements. Moving away from a one-sided focus on static DNA, the path towards health and disease of each individual is now firmly conceptualized as a process of gene–environment interaction (GxE), where the ‘environment’ includes ‘psychosocial’ factors and the organism as a whole (Bousquet et al., 2011). In this picture, both disease and health are dynamic, functional states of the system that *emerge* through the GxE process; they are different aspects of a single continuum of potential network states in space and time (see Paper II and figures therein). Diseases may be defined in terms of abnormal network states and health in minimal terms as normal network states (see Fig. 3 and 4 in paper II). Multi-morbidities are different, but related expressions of perturbations in this network.

At least *as a vision*, in its theorizing, P4SM quite explicitly takes biomedicine from conceptualizing health and disease as resulting from linear relationships between parts and

wholes (a 'gene-centric' view) to a multi-causal, non-linear 'network-centric' view of persons, health and disease (see paper II). On a theoretical level this means that systems medicine may contribute in counteracting the challenge of fragmentation, linearity or specific etiology described in the Background, and, as such, for understanding patients as persons.

7.1.2 Downward causation and biological relativity

What more has P4SM to offer theoretically in explaining how parts relate to parts, wholes relate to parts, how "bio" relates to "psycho" and "socio"? How can it take primary care medicine further in conceptualizing the whole person?

As argued in papers I and II, the deepest theoretical contribution of P4SM may be that it *slowly* (by no means radically at this point) moves biomedicine from the one-dimensional molecular focus of molecular biology towards a systems view where no level is causally or epistemologically privileged. Among the systems biological concepts, I argue that *downward causation* and the related concept of *biological relativity*, discussed by systems biologist Denis Noble, offer the greatest potential (see paper I). It is significant that his argument is scientific in the sense that it is sought developed *within* the confines of a general scientific worldview of naturalism and materialism.

Very generally, downward causation means that the whole, with its emergent properties, has some sort of causal or constraining influence over the parts by which it is constituted (see Definitions and Key concepts). In the philosophy of Noble, structural and environmental conditions (boundary conditions) *constrain* or *organize* the behavior of the components.[32] The environment and the environmentally situated person or organism exerts a higher-level control of gene expression. The significance of his philosophical emphasis on this concept is that it counteracts the one-sided focus on "upward causation" in the traditional biomedical model and genomic personalized medicine (see Background, section 2.1). According to Noble,

[32] Noble, who is central to this thesis, defines downward causation primarily "in terms of the influence of boundary conditions determined by a higher scale" (Noble, 2012a, p. 5). He uses the term "'boundary conditions' in a general sense here to refer to all the structural and environmental conditions that constrain the behaviour of the components" (Noble 2013, p. 4). In other words, his concept of downward causation seems to fall into the *medium* category of downward causation described under Definitions and Key concepts. However, Noble also uses the concept of an attractor, and thus he may also rely on the *weak* idea. Noble also states that his idea of downward causation conforms to the idea of supervenience, see also Definitions and Key concepts (Noble, 2013, p. 5).

there is no *a priori* reason to say that the lower levels, or smaller scales, are causally more important than the higher/larger. This is the principle of *biological relativity*, "the relativistic principle that there is no privileged scale of causality in biology" (Noble, 2013, p. 1). Noble also, of course, acknowledges "upward causation", so the result causality that defines organisms is not "downward causation" only, but metaphorically a circular "both-way"-causation (see **Figure 3**).

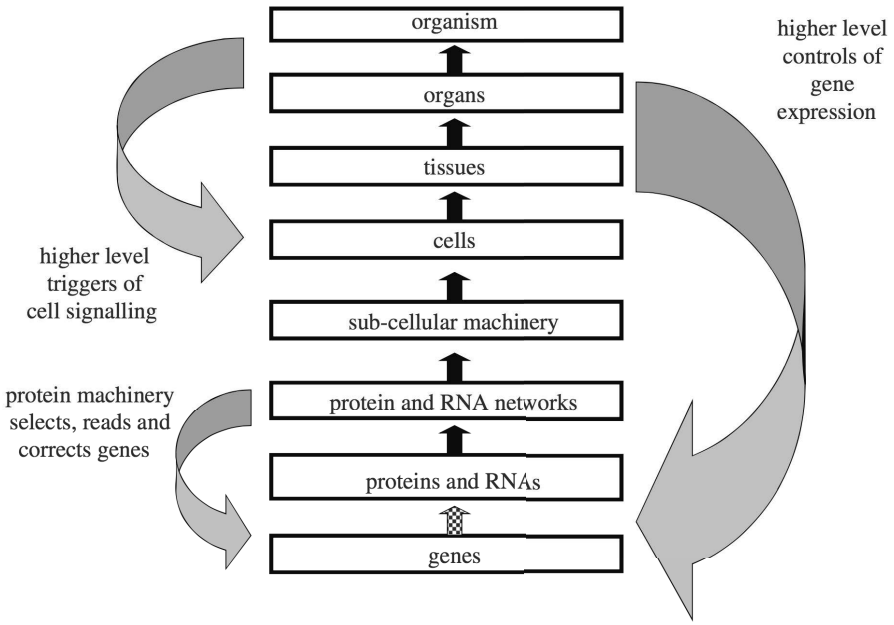

Figure 3 Denis Noble´s depiction of "downward" and "upward" causation (reprinted from Noble, 2013, adapted from Noble, 2006). Used with permission.

Causation is key to science and medicine. Different aspects of human life are considered more important if they are considered causally important (see Causation in Definitions and Key concepts). Upward causation renders the whole person or the "psychosocial" *epiphenomenal*, causally impotent (see Definitions and Key concepts). Since the whole is ontologically portrayed as "nothing but the parts", the person or "psychosocial" factors may be perceived as epistemologically *ignorable* (see for example Deacon, 2012, p. 12; Velmans, 2009, p. 305). With regard to the challenge of fragmentation Noble´s important contribution is that the person or the self should *a priori* be regarded as causally no less important or concrete than

the molecular. The person – or self – becomes an integrative process that constrains or organizes lower level processes. I conclude that this may be important in reinstating the person as an agent, both in biomedical, personalized medicine and in primary care. It may add more conceptual weight to the significance of whole person care, of social relations and environmental factors – without departure from science. Viewed as one element of systems medicine´s technoscientific holism, the concepts of downward causation and biological relativity may thus also contribute to bridging the gap between the sciences and humanities in medicine.

However, it is important to note that the concept of downward causation is very controversial in science and philosophy, and it is not clear how it should be understood (see discussions in Carroll, 2011; Emmeche et al., 2000; Noble, 2012a; 2013). As I also noted in my paper I,

> "If persons are to be considered their own self-organizers and constraints, it is important to note that these concepts do not as yet explain the difference between living agents and non-living entities (Keller, 2007). For example, it is difficult to know what kind of agency or will is granted to humans when looking at them as their own self-constraints. Concerning the concept of attractors as a metaphor for goal-directedness, one must also note that attractors are rule-governed in a way that human beings may not be (Strand et al., 2004)".

Downward causation should thus be seen as a concept in development that reflects key developments in conceptualizing life (Ellis et al., 2012). Doctors should, for example, not be hasty in using it to justify the agency of the patient-as-a-person.

7.1.3 The whole person conceptualized as predictable and controllable

It is crucial to realize that, while Noble is one key visionary, his theory is not mainstream. Rather than involving a holism as in humanistic medicine, the holism of mainstream P4SM is created to enable computers to model human beings, their health and disease. The "holistic" theory of P4SM is also mainly chosen in order to fulfill the traditional scientific goals of mechanistic explanation, prediction and control, which in turn leads to fulfillment of both the stated and unstated goals of medicine as well as industrial commercialization. In my material, I have found no indications that mainstream P4SM represents a departure from these goals. Systems medicine as a movement generally just reflects the realization that in order to obtain these goals, a more complex, all-encompassing approach has to be taken. In order to do so, P4SM brings an engineering mindset to biomedicine: P4SM is in the process of making

biomedicine more scientifically rigorous, more technologically dependent, more quantitative. These goals constrain its holism or integrationism. Mostly, although it surely involves discussions on how to conceptualize living entities, P4SM upholds the machine metaphor in biomedicine. The machine we model ourselves according to just becomes more complex, passing from 'clockwork' to 'computer' towards artificial intelligence. While the predictive models of previous predictive medicine have so far not ushered in a revolution in disease prevention, the hope is that P4SM can deal with multi-causality and thus overcome difficulties in predicting the behavior of complex systems and establish more clinically valid risk estimates at the individual level.

On the theoretical level, this is the essence of technoscientific holism: Although the whole life process of each individual is defined as complex, this whole – and the whole continuum of health and disease states it may be in – is defined as potentially quantifiable, predictable and controllable. While the holism of humanistic medicine has exercised a certain tolerance towards disease and death, the inevitability of dying and the possibility of health being compatible with disease are not mentioned in our material, technoscientific holism is constructed to support an ambitious quest for control.

7.2 Technoscientific holism entails holistic medicalization

A major finding in this thesis is that the technoscientific holism of P4SM entails the most radical medicalization of human life in history. I call this "holistic medicalization", a far-reaching example of a broader trend – "*the medicalization of health and life itself*" (see paper II and Background). This "holistic medicalization" of P4SM can be divided in "medicalization in theory" and "medicalization in practice".

7.2.1 Holistic medicalization in theory

A key element of medicalization is the definitional process itself, the process of defining an aspect of life in medical terms *as controllable*. I argue that, when a person as a whole system and its whole continuum of functioning from disease via risk states to positively defined health are *defined in* quantitative, medical terms and as controllable, medicalization becomes

holistic on a theoretical level. It is holistic in the sense that it is *all-encompassing*. Holistic medicalization does not primarily entail that aspects of life are defined *as new diseases*. Rather, it puts wholeness and health itself under medical jurisdiction, pointing toward a situation in which 'life itself' is controlled.

Here, a point made by Raymond Downing is particularly important for my argument: Although many GPs familiar with humanistic medicine may connote *holism* with *anti-medicalization*, systems thinking may lead to *more medicalization*. The reason is simply that it opens up for *the whole to be medicalized*. Systems thinking and holism is, in an important sense, *all-encompassing*. As Downing states: "This (…) is what systems thinking does: it tries to bring all aspects of an endeavor – all the people, machines, processes, and information – together; it tries to capture *everything*" (Downing, 2011, p. 73). In P4SM systems thinking leads to an advanced instantiation of what Downing calls *biohealth,* "the sort of health and wholeness that results from applying the biological sciences" (Downing 2011, p. 6). This holism induces us to control *all aspects* of a phenomenon (e.g. a person's life).

I also argue that the more *holistic* P4SM will become in its technoscientific sense, defining 'the whole' as actionable, the more medicalization will result. As the major "rate-limiting" hindrance to medicalization is biocomplexity, and P4SM models will likely define biomedicine's uttermost efforts to overcome this complexity, it will also delineate the degree to which life can be technoscientifically controlled. Having the ability to predict and control the totality of health aspects will logically also mean *total* medicalization. The endgame of medicalization will result from trying to piece all bodily parts and subsystems together to define and control life *in toto*. I will return to this totalizing aspect of systems medicine in the discussion.

7.2.2 Holistic medicalization in practice

In practice, P4SM may be seen as the culmination of a series of increasingly expansive efforts to deal with the complexity of human biology in order to improve practice, especially predictive and preventive strategies (see papers II and III). As envisioned, the technologies supporting P4SM allow both diagnostics, prognostic and therapeutics to be both multi-level (including the 'psychosocial' levels and so-called lifestyle), continuous throughout the life

course and directed at all types of network states, all along the continuum from overt pathology, via more or less well-discerned risk profiles, 'normality' and into the positive 'wellness space'. In terms of diagnostics and prognostics this regime of monitoring aimed at the earliest possible detection of disease and risk factors represents *a novel form of continual screening of unprecedented scope* where "life itself" is continually screened.

The way holistic medicalization may turn out in practice is illustrated by the pioneering "Hundred Person Wellness Project" (HPWP). Here 100 % of the participants were labelled with one or more "actionable possibilities" or as "at risk". This represents a continuation, a totalizing endpoint, of a historical development (see Paper III, section 2 and references therein) where biomedicine has labelled an increasing proportion of the population as in need of medical attention.

7.2.3 Participatory medicalization

As envisioned, P4 medicine is also a system that expects active participation of the whole of society and individual citizens. I argue that this participatory aspect of P4 medicine can also be viewed as an aspect of holistic medicalization. I call this *participatory medicalization*. Technology is becoming democratized. In the P4SM vision, the concept of "democratization" is thereby given a new meaning where technology is proposed to allow people to *know themselves and take control* of their lives through this knowledge. However, to the extent that people will gain—or lose—genuine control, they will do so according to the metrics and goals of P4SM, giving its proponents considerable definitional power. What is most evidently "democratized" is the ability to *self-medicalize*, and now more 'holistically' than ever. At the same time patient participation is necessary in order to realize P4SM's holism and goals of prediction and control, meaning that its implementation is clearly not only intended to empower individuals. The participatory "P" of the P4SM vision involves what Rose & Rabinow, building on the philosopher Michel Foucault, call *a mode of subjectification*...

> ...through which individuals are brought to work on themselves, under certain forms of authority, (...) by means of practices of the self, in the name of their own life or health, that of their family or some other collectivity, or indeed in the name of the life or health of the population as a whole (Rabinow and Rose 2006).

While the emancipatory potential of medicalization is very visible in the P4SM vision, freedom from disease and "democratized" care, this subjectification remains invisible.

7.3 The overall utility of systems medicine as a proposed framework

In this section, I will present the results from the next step in critically evaluating P4SM as a proposed framework for future primary care medicine (Paper III). Advocates of P4SM promise *a revolution in clinical utility*, especially in predictive and preventive medicine, *through its holism*. To predict with certainty how the overall utility of P4SM will turn out in the future, is of course impossible. However, making such predictions is precisely what advocates of P4SM do when they make their promises. Hood and colleagues (2015, p. 3), for example, insist that the benefits of their approach will "far outweigh any possible harms".

I have defined medicalization as something that is not inherently wrong, but as action that always comes with risks of potential waste and harm. As described above, the holism of P4SM entails an unprecedented "holistic" medicalization in the form of a multi-level screening process of unprecedented scope. While leading journals are campaigning against "Too much medicine" and for a "Less is more strategy" (BMJ; JAMA Internal Medicine), P4SM proposes to tip the balance of benefits and harm in primary care-based preventive medicine through *even more medicine*. This "more medicine" inevitably comes with downsides of waste and harm. An underlying premise for the overall balance of benefits vs. waste and harm to turn out positive in P4SM is thus that its radical medicalization, can be weighed up by very significant gains in the overall utility of preventive medicine. For P4SM to work in practice it must somehow turn *more* (measurements, more medical intervention) into less (waste and harm) by creating integrative models that register only that which is actually significant. This is a momentous challenge. Utility and actionability of medical testing presuppose not only that the early detection of disease and risk assessments have a high clinical validity (accuracy), predictive and prognostic power, but that they can be coupled to actions that show clinical efficacy and effectiveness as well as an adequate balance of benefits and harms in a wider clinical and societal context (see Definitions and Key concepts).

As stated in Background, the challenge of primary care medicine is to achieve the possible utility *in the widest sense*. As presented in paper III, my prediction concerning P4SM´s corresponding promise is based on three converging lines of argument: The first is based on challenges facing predictive and preventive medicine, both before and after the introduction of genomic information in risk algorithms, the second concerns limitations of technoscientific holism in counteracting fragmentation and creating better risk predicting algorithms, and the third concerns the fact that even predictive algorithms coupled to effective interventions may not be useful as people will not necessarily participate as predicted. On the whole, preventive strategies such as implementation of preventive clinical guidelines, general health checks, screening and lifestyle counselling, have previously shown limited effectiveness in practice (see references Paper III).

7.3.1 Problems of integration, predictability and controllability

In the papers of this thesis, several limitations of the holism of P4SM have been noted, both conceptually and methodologically. These are significant when evaluating its wide-ranging promises of a revolution in clinical utility of preventive medicine. The limitations can be summarized as problems of integration, predictability and controllability (see Definitions and Key concepts for "predictability" and "prediction").

Problems of integration: The overarching promise of holism in P4SM is to counteract fragmentation. As outlined in the background, integrationism and holism are the premises on which P4SMs visions rely. However, while it promises integration, the first thing P4SM contributes, is the most profound *fragmentation* in medical history in terms of *billions* of molecular and other fragmented data-points that need to be integrated and made sense of. I find that P4SM shows limitations in tackling this fragmentation, thus risking instead to aggravate the problems it promises to solve.

Firstly, the main strategy of P4SM in personalizing medicine is stratification. Dividing disease categories into even smaller categories, defining norm and deviation for each of them, each category with a guideline, may itself lead to further fragmentation unless the links between these categories can be elucidated and an integrative management suggested.

Other main challenges concern the integration of bodily parts and associated data points. One main challenge is that the amount of 'noise' inherent in the data increases as big data are collected, and handling and integrating large amounts of data pose a number of substantial challenges, both technical and associated with the (causal) biocomplexity involved.

Some of the challenges are conceptual. In seeking to connect parts to wholes, P4SM faces deep philosophical issues, such as "what is life" and the "mind-body problem". As concluded in papers I and II, systems biologists do not fully know how to faithfully conceptualize their subject matter: *living wholes*. Systems biologists are aware of this fact (see e.g. Gare, 2013; Omholt, 2013; Rosslenbroich, 2011; 2016; Saetzler et al., 2011). However, we do not know how this endeavor will turn out, meaning that P4SM and its preventive efforts may be based on a flawed conceptual foundation.

I find that the purported holism of mainstream P4SM is in fact a form of reductionism "in disguise". Firstly, *all modeling* involves reduction of some sort. Modeling in P4SM is about creating an abstract simplification of human health that at the same time enables prediction and control. Secondly, mainstream P4SM is still strongly focused on networks of molecular parts, and seems to continue the traditional emphasis on *upward causation*. However, systems medicine should be taken very seriously as the science that not only has to study how parts interact, but how the environmentally embedded organism as a whole constrains the parts (i.e. *downward causation*). An increasingly rich biological literature from fields such as psychoneuroimmunology, epigenetics, psychosocial genomics, developmental biology and epidemiology documents how social and personal (psychological) experience of each individual affects the cellular and molecular levels (see references Paper III as examples). Advocates of P4SM also appreciate the importance of psychosocial and other environmental factors. However, Sara Green and I argue in Paper III that it is becoming increasingly clear that there are serious practical and principal limitations to the idea of bridging the gap between genotypes and phenotypes. Serious challenges are met in modeling the whole system where there are complex feedback relations between molecular and social factors and adaptation to extremely complex social interactions (i.e. downward causation). The concept of downward causation or downward "control", which highlights the importance of a complex environment, thus also highlights challenges of integrating and making true causal sense of the fragmented data. If one takes the importance of organism-level and environmental constraints seriously, systems medicine likely also has to account for specifically *human*

constraints, including the actions and thinking of human organisms and an ever-changing social and environmental context. However, one cannot assume that one can measure and integrate every factor that influences human health and disease through life in its models and reflect the true human biocomplexity. If these factors are causally significant – and we have no reason to assume that they are not – an account of *all components of disease complexity*, which is what P4SM promises (see e.g. Bousquet et al., 2011), thus seems outside its scope. The significance of the following statement, which Denis Noble himself takes from Sulston and Ferry (2002), is therefore hard to overstate: "*The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms"* (Noble, 2010).

Problems of predictability and controllability: Although the future is unknown, the above described problems of integration and truly accounting for the complexity of human wholes and "holistic" sets of big data, may well have highly significant implications for P4SM's ability to predict disease. The promises of a revolution in predictive and preventive medicine in P4SM depends on the extent to which human biology, including the aspects we call "psychosocial" are predictable and controllable at all. Moreover, the promise of predictive medicine through holism raises equally fundamental questions about the deterministic nature and/or predictability of complex systems in general. The sum of the fragmented measurements in P4SM may thus add up to an unmanageable amount of isolated considerations, diagnoses, risk assessments, treatments and considerations, each with a risk of waste and harm.

7.3.2 Direct and indirect harm (opportunity cost)

The most obvious possible harm is that, which results from being labelled as at risk or diseased. While more research is needed, there is evidence of negative psychological effects of false positives in population screening programs (see references in Paper III). Medical testing and being labelled as "at risk" may involve consequences such as health damage, anxiety, decreased quality of life, a changed self-image or lost job opportunities. A "holistic medicalization", which involves continual focus on medical risk in a previously well population, very obviously will involve significant harm. Fundamentally, if one takes health

to mean the ability to "forget that one is healthy" (Gadamer, 1996, p vii), one may deduce that the constant, all-encompassing health focus of P4SM would make it virtually impossible to feel healthy in this sense.

However, direct harm is not the most obvious damage that will result from P4SM. Given the expansiveness of the P4SM endeavor, I argue that *indirect harm* and cost may be just as important and even more inevitable. Even if problems of prediction, overdiagnosis, false positives and findings of unknown significance were nullified, the sheer amount of work done by all involved agents in the population and healthcare system would represent a significant distraction of attention and economic resources away from other problems, potentially hindering their productive solutions (opportunity cost). People could simply do quite productive work with the energy, time and money that goes into focusing on their own health. Relatedly, the people working in healthcare can be distracted away from other useful actions (for example patients who have become gravely ill) when they have to consider the incoming data deluge from P4SM and the questions it brings with it.

7.3.3 Social and cultural iatrogenesis

In a way that is hard to measure, P4SM may also lead to what Ivan Illich (1975) called social and cultural iatrogenesis: Displacing other valid goals, values and ways of understanding and tackling life, distort our understanding of problems that should be understood on the personal, social or political levels by describing them in reductive or engineering terms. A medicine based on quantitative P4SM might denigrate aspects of the 'the good life' that its metrics cannot capture.

While P4SM promises democratization of medicine and allowing people to take control over their lives, it may arguably also lead to *less* freedom. As pointed out in my argument on *participatory medicalization*, participants will be expected to follow the metrics and values of P4SM in a massive endeavor of individualized self-control. Responsibility for not only private, but also public health, would fall on individuals to a degree never known before.

7.3.4 Drivers of waste and harm

In the literature on waste and harm in medicine a number of factors have been identified as drivers of waste and harm (Bodenheimer, 2005; Brodersen et al., 2014; Callahan, 1998; 2008; Dybczak & Przywara, 2010; Fisher & Welch, 1999; Heath, 2013b; Hofmann, 2014a; Moynihan et al., 2012; Welch et al., 2011):

As presented in paper III, my material shows that P4SM is associated with most if not all these "risk factors". First and foremost, it is associated with new technology that allows measurements and discovery of more, increasingly subtle, abnormalities, as well as new therapeutic action with potential side effects. It focuses specifically on early detection of disease and risk as well as early intervention in people who currently feel well, a focus on individuals rather than populations, screening, a widening of the scope of medicine, lowered thresholds for what is considered disease or "actionable" in medicine, the cultural belief that more medicine is better, the cultural belief in new technology and progress, the creation of high expectations to what medicine can achieve, health perfectionism, health consumerism, good intentions and professional and economic vested interests (e.g. the promise of a lucrative "wellness industry").

7.3.5 Findings of unknown significance, false positives, overdiagnosis

As outlined in paper II and III, main factors in the development of waste and harm in medicine that result from the above described drivers are findings of unknown significance, false positives and overdiagnosis. Based on past experience of predictive medicine, including personalized genomic medicine, one may predict that screening for risk factors, an extreme focus on early detection of disease in asymptomatic people, an increasing amount of data, sensitive technologies that provides an increased capacity to pick up bodily abnormalities and as well as widening definitions of what is "actionable" will aggravate these problems. The main premise of P4SM is that such problems can be overcome through integrative computational modeling that counteracts fragmentation and leads to more accurate risk prediction algorithms. However, as already argued, P4SM faces fundamental problems of integration and prediction.

7.3.6 Limits to patient participation, compliance and motivation

A key premise for P4SM to work in practice is that people will actually comply with its recommendations and respond to risk assessments with sustained lifestyle changes. As argued in paper III, this has been a main problem of previous preventive strategies. Previous studies show little or no effect of risk information from personal genetic risk profiling on health-related actions, and a recent randomized controlled trial, providing patients with an extensive self-monitoring system showed no short-term effects on health care utilization or costs (see Bloss et al., 2016 in Paper III). Although advocates of P4SM predict that constant monitoring will change patient engagement, research to support this has not been published and we have no guarantee that this will actually come to pass in the general population. It is simply not obvious that people´s values align with ”P4 values” of prediction and control and that the population is motivated. It is also highly unclear if studies recruiting ”health enthusiasts” such as those volunteering in the HPWP project or engaged in the ”quantified self” movement, are reasonably representative of the general population. Additionally, even if people *would* take more control over their lives and health, this will also not in itself change socioeconomic factors that are vital for shaping public health.

7.3.7 Conclusion on the future overall utility of systems medicine

As stated in Paper III, the benefits of P4SM's holistic medicalization are not inevitable, while costs and harms, to some degree, are. My argument is not that P4SM will not be able to provide some or many useful predictions, as well as benefits through prevention. However, what is promised in P4SM is a *revolution* in the practice of medicine. My main argument here is that there is a clear discrepancy between these far-ranging promises on the one hand and the limitations and uncertainties of technoscientific holism in tackling the complexity involved and predicting and controlling future health as well as risk of waste and harm on the other. Holistic medicalization seems to require very significant benefits for the balance to turn out positive. So far, the conceptual grounds and empirical evidence suggesting that this will actually happen is very limited. I thus find good reasons to be highly skeptical of the promises of P4SM in offering a revolution in preventive medicine through its new holism. This raises important questions as to why the promises are made so boldly. The burden of proof should thus weigh heavily on its visionaries.

8. Discussion and implications

In this chapter I will elaborate my argument and put it in a wider perspective. In addition, I will discuss strengths and weaknesses of the thesis and reflect upon future research needed.

8.1 Systems medicine redefines holism in medicine

8.1.1. An appropriation of words

As stated in the Results chapter above, a main finding in this thesis is that P4 systems medicine (P4SM) redefines the meaning of *holism* in medicine. I want to start this discussion by elaborating how this represents a continuation of an ongoing redefinition of the concept of *personalized medicine*.

The idea of a medicine that is *personalized* has been with Western medicine since its inception as a key value and goal. The concept has often been tied to the name of Hippocrates (ca. 460-375 BCE) who is quoted as proclaiming that, "it is more important to know what sort of person has a disease than to know what sort of disease a person has" (Yurkiewicz, 2010). I think it is important for the reader to know that the concept of personalized medicine was from the beginning about *the whole person*. It was inextricably tied to *holism*. As noted in the Background, holism has in turn arguably always been tied to *systems thinking,* understood very broadly. In the case of Hippocrates, for example, the systems thinking lay in seeing health and disease as products of interactions between different forces of nature or the bodily fluids (blood, phlegm and black/yellow bile). Theoretical biochemist and historian G. Rickey Welch notes about Hippocrates in a paper on systems biology that…

> "It was he who produced the first systemic view of the human organism and, by inference, life forms in general. One finds in the collective works of Hippocrates and his followers (the so-called ''Hippocratic Corpus'') the resounding belief that knowledge of the living being requires a focus on the properties of the whole, not the parts" (Welch, 2009, p. 8).

In one sense then, we find in ancient Greek medicine, personified by Hippocrates, the joint precursors of personalized medicine, holism and systems biology.

However, while this amalgam of ideas has been welded together throughout medical history, the dual ideas of personalized medicine and holism have for the last 150 years mostly existed

as a humanistic complement or reaction to the universalism and growing mechanistic reductionism of scientific biomedicine. In the 19th Century this complementary humanism was highlighted by William Osler, otherwise a pioneer of scientifically based medicine, who echoed Hippocrates' "It is more important…etc" (cited in Stange, 2009b). Osler also stated that, "If it were not for the great variability among individuals, medicine might as well be a science and not an art" (cited in Tutton, 2012, p. 1721). From Osler we can then trace the ideas of holism and personalized medicine to the *patient-as-a-person movement* in the interwar period and the decades that followed (see Section 1.3, Peabody, 1927; Robinson, 1939; see also Kunitz, 2002; Tutton, 2012; 2014, chapter 1). This "whole person" thinking has been especially dear to the medical generalist. The first article that pops up when searching the PubMed database for "personalized medicine" is, for example, a paper by W.M. Gibson from 1971 in Canadian Family Physician entitled "*Can personalized medicine survive*?" The paper defends whole person care in the machine-world of biomedicine. Holistic definitions of health in the philosophy of medicine, for example that of philosopher Lennart Nordenfelt, relatedly rest on the claim that, "Health is a concept which basically pertains to the whole person" (Nordenfelt, 2007, p. 7). Today this amalgam of humanism, personalized medicine and holism is manifest most visibly in what philosopher James Marcum (2008) calls "humanistic medicine", for example the biopsychosocial model[33], patient-centered or *person-centered medicine* (Engel, 1977; McWhinney & Freeman, 2009; Miles & Mezzich, 2011; Sturmberg, 2009). Importantly, these concepts also draw on systems thinking, highlighting the recurring, close links between humanism, personalized medicine, holism and systems thinking.

Today, the idea of personalization is undergoing a so-called creative destruction, a technologically driven disruption (Topol, 2012). Starting with the Human Genome Project in the 1990s, the mainstream meaning of "personalized medicine" has changed rapidly. The traditionally humanistic concept has been adopted by technoscientific biomedicine and redefined according to its conceptual needs, goals and values (Jain, 1998; 2015). In this context the term has been used to promote the way cutting edge genetics was to be applied to human health. At first this *technoscientific,* personalized medicine was reductionist as in

[33] It should be noted that biopsychosocial medicine is a concept that has been used by a number of authors (e.g. Wessely et al., 2005), and may sometimes be taken merely to be an inflated version of the biomedical model, applying the same scientific philosophy and methods on all levels, with few remnants of systems thinking. I refer to it as originally proposed by George Engel (1977, 1980, 1997; see also Borrell-Carrió et al., 2004).

gene-centric and strongly molecularly focused. This is in line with the traditional, dominant biomedical model, which focused on diseases linked to organ systems or bodily parts (Marcum, 2008). This development has been eloquently outlined by sociologist Richard Tutton in his book, *The genomic reimagining of personalized medicine* (2014).

It is crucial to note that the motivations behind the traditional, humanistic personalized medicine, and the new technoscientific, personalized medicine are different. The former has been a reaction to the perceived dehumanization inherent in scientific biomedicine, and emphasizes the human doctor-patient relationship and aspects of human biology that can only be known in this context like individual narratives, experience, agency and values. The latter, by contrast, *is* scientific biomedicine and geared towards mechanistic understanding, prediction and control through technology. As Tutton puts it, the meaning of "personalized medicine" was rearticulated from "being a matter of a relationships or interaction between human beings" to being "mediated through sophisticated technologies" (Tutton, 2014, p. 55).

While the key goals of prediction and control remain the same as previous "one-size-fits-all" biomedicine, personalized biomedicine represented an important epistemological shift: Where biomedicine has traditionally seen variation among individuals as a source of bias to be corrected for, scientific personalized medicine began to conceptualize it differently: As an avenue towards *more* accurate predictions and *more* effective medical control (Tutton, 2014).

Although nobody can really claim exclusive ownership to a concept like personalized medicine, this redefinition will from the perspective of the humanistically inclined medical generalist be seen as an appropriation – or biomedicalization – of the humanistic concept of *personalized medicine*. Once appropriated, the concept of personalized medicine lends to the biomedical quest a host of positive connotations.

8.1.2 Holism: The continued redefinition of personalized medicine

The current thesis takes the history of personalized medicine a step further. What it essentially shows is how systems medicine, the post-genomic heir to genomic medicine, the new vanguard of biomedical technology, continues the above described redefinition of personalized medicine by appropriating the "whole" in "personalized". Its title could alternatively perhaps have been "The post-genomic reimagining of holism".

In short, the *continued reimagining* of personalized medicine goes like this: At first, technoscientific *personalized medicine* was reductionist as in "gene-centric", in focusing mostly on segments of DNA and their (presumed) relatively linear relationships to the whole phenotype. In light of the abovementioned history of personalized medicine, where personalized medicine and holism were amalgamated, this "personalization through reductionism" may be seen as an historical anomaly. Parts-focus and personalization are uneasy bedfellows. A main lesson of the Human Genome Project is to reaffirm this ancient medical truth: The whole cannot be known through parts in isolation. As this message sinks in, systems medicine is again moving personalized medicine and the biomedical model back towards Hippocrates' original, *holistic* understanding of personalized medicine, but this time around recast in an image enabled by technology.

I have very generally defined personalized medicine as a form of medicine that can account for those factors that define health and disease in each particular person (i.e. variability among persons) in order to improve practice. This is a definition that encompasses all forms of personalized medicine. With regard to this definition, "*those factors that define…"* are now explicitly conceptualized, or envisioned, as pertaining to whole systems.

Personalized medicine is about counteracting the downsides of *universalism* in medicine (see Background, section 2.1). While early gene-centric personalized medicine attempted to counteract *universalism* by focusing on the genomic level only, systems medicine appreciates that personalization must ultimately be achieved at the level of life itself. In 1992, molecular biologist Walter Gilbert sought to rally resources to the sequencing of the human genome by calling the human genome "the holy grail" of biomedicine. In contrast, systems biologist Denis Noble dismisses the genome as the Book of Life, and simply states that, "the Book of Life is life itself" (Noble, 2006, p. 10). As I hope to have shown in the papers of this thesis, this change in where the biomedical holy grail resides holds both potentials and pitfalls. It is not in your genome anymore. It is you.

8.2 Conception of persons: biological relativity and downward causation

The work of this thesis began, in paper I, with a focus on the elements of the philosophy of systems medicine that I found most constructive in developing the theoretical foundation of

primary care medicine. This led me to focus on the philosophy of systems biologist Denis Noble. The systems biological concepts that I find to hold the greatest potential in "re-imagining" the person in medicine are *downward causation* and *biological relativity* i.e. that wholes causally constrain or organize their parts and that no level of biological organization should be regarded as causally or epistemologically privileged *a priori* (Noble, 2012). I argue that these ideas may reinstate the person as an ontologically real, causally potent and epistemologically significant entity in biomedicine. Taken seriously, this could have profound consequences, lifting the profession´s gaze from the molecular 'soup' to the actions and experience of living persons in theory and perhaps in action (see for example Sturmberg, 2016 for a systems biological view of multi-morbidity).

At the same time, it may be rightly asked if the concepts of downward causation and biological relativity (or related concepts such as self-organization) bring something wholly new to biomedicine. The idea of downward causation itself is certainly not new (see for example Emmeche et al., 2000). George Engel and Ian McWhinney, as important examples in medicine, drew on systems theorists and biologists Ludwig von Bertalanffy (1901–1972) and Paul Weiss (1898–1989) in developing their biopsychosocial and patient-centered thinking. Weiss, for his part, highlighted what he called *macrodeterminacy* (as opposed to causal reductionism or microdeterminacy) (Drack & Wolkenhauer, 2011). Bertalanffy conceptualized the person as "an active personality system", a spontaneously active, adaptive, goal-directed, purposeful, creative, self-aware organism, which is open to the environment and defined by symbolic interaction and language (see for example Bertalanffy 1969, p. 44 and 208). Drawing on Bertalanffy and Weiss, Engel and McWhinney also refer to two-way causation in hierarchical biological systems in their publications (Engel, 1980; McWhinney & Freeman, 2009, chapter 5).

Conceptually, there may thus be few fundamental differences between earlier systems theory and biology and today´s emphasis downward causation or multi-level causality (see e.g. Wolkenhauer & Green, 2013). So, what is new and relevant about Noble´s philosophy and systems medicine for the theoretical foundation of primary care? It is that this form of thinking, previously associated with a humanistic "fringe" of medicine, is now considered relevant in discussions forming the cutting edge of its real powerhouse: Technoscientific biomedicine (Boissel et al., 2015). The contribution of Noble and the key systems medical concept of multi-level causality is to bring these discussions into the mainstream of

biomedicine, to further their development and to give them scientific and mathematical substance and thus more conceptual weight.[34] Through its focus on multi-scale modeling of biological systems, philosophical discussions on the nature of the living organisms (e.g. downward causation) are reinvigorated.

To put this in perspective, take a chapter on the theoretical basis of the biopsychosocial model in a decade-old textbook, authored by philosopher Helge Malmgren (2005). Malmgren´s primary concern is that Engel, and his reference to systems theory, does not detail the mind-body relationship. It does not specify just how the interactions between different levels (.e.g "social", "personal" and "biochemical") happen. He states that the model should be freed from systems theory, because "it does not add any power to the model". The development of systems medicine challenges this statement. Although it is not at all clear if it can "solve" the hard problem of what "mind" is or how "it" relates to "body", systems theory in the form of systems medicine is likely to add to biopsychosocial or holistic thinking. This may not happen in the way expected by early proponents like Engel, but it can certainly not be dismissed as having no potential for adding power to the model. Moreover, although they are not always working as mathematical modellers, I find that it is theorists and scientists (including systems biologists) who employ forms of systems theory who are taking the conception of life further at this point in the history of biology, with considerable potential for theory development in medicine (see e.g. Bickard, 2013; Deacon, 2012; Ellis et al., 2012; Gare, 2013; Kauffman, 2008b; Juarrero, 1999; Omholt, 2013; Rosslenbroich, 2011; 2015; Ruiz-Mirazo et al., 2010; Thompson, 2007). Such theorists may also influence systems biologists.

It may of course be that, in time, the concept of downward causation may be found to be useless and misguided, as argued for example by physicist Sean Carroll (2011). However, in the meantime, its current function is to contribute to fundamental theoretical reflection in medicine as to how we should understand the phenomena clinicians are dealing with on an everyday basis. This may in itself contribute to counteracting fragmentation in medicine.

A complete discussion of the concept of downward causation, its potentials and limitations, has been beyond the scope of this thesis. So has a discussion of the concepts of "causation", "personhood", "mind" and "self", each of which are associated with much philosophical debate. I only treat one way of conceptualizing "downward causation", that of Denis Noble. It

[34] Noble has for example edited a whole volume in the journal Interface devoted to the concept of downward causation. The idea is very clearly that biomedicine needs new thinking (see Ellis et al., 2012).

should also be noted that Noble mostly uses the concept in conceptualizing living systems in general and not in describing the person, the self or the mind. The latter use is only a part of Noble´s philosophy treated explicitly only in a few publications (Noble 2007; 2008; 2013; Noble et al., 2014). This does not add up to a complete or detailed philosophy of mind or personhood. Noble´s theorizing only brings the concept of downward causation in relation to our philosophy of the human organism, and only opens doors for further conceptual innovation. I am also aware that it is controversial and somewhat vague to talk of concepts like meaning, value and symbolic interaction as "constraints" on human health or "downward causation" as a metaphor for intentionality or agency of human organisms. However, at the same time, I am not merely inventing this kind of thinking (see e.g. Juarrero, 1999; Deacon, 2012). Downward causation represents an appreciation that something is missing in biology´s conception of life. It is an attempt to fill this void; it is thinking in development, no finished theory.

8.3 Technoscientific appropriation of holism and medical humanism

I started out very fascinated about the theoretical deliberations and promises of systems medicine, but as I studied it in detail, I grew increasingly skeptical of its purported humanism. Seen from the point of view of humanistically inclined general practice (the tradition associated, for example, with Ian McWhinney in the 1990s), the great paradox of today's systems medicine, I think, is this: Just when biomedicine moves in a direction that is more sophisticated theoretically than earlier molecular biology, just when there is an appreciation of the need for a holistic systems approach, the result is *more* control, more medicalization and potentially more dehumanization of medicine. It is a paradox, for both past humanistic medicine and new systems medicine are sensing and trying to mend the same problem: fragmentation. Coming from different angles, they are kindred in grappling with the same brokenness of the organism. However, their holisms end as opposites.

It should be noted that holism or systems thinking must not necessarily result in "holistic medicalization". It must be coupled to an ambition to take control. It could be coupled to a view of the body as unpredictable and uncontrollable, and to tolerance of the body´s weakness, frailty and the inevitability of disease and death. In P4SM it generally is not. It is holism *in combination with* the continued aim of scientific prediction and control that leads toward

holistic medicalization. I refer the reader to Sagner et al. (2016) for a recent and very telling expression of this development, in which the concept of a "P4 Health Spectrum" is launched. This development should perhaps come as no surprise. I have already pointed out in the Results chapter how systems thinking and holism may inherently lead medicine to incorporate more elements into its models, to become more and more all encompassing. This point is in fact older. Physician-philosopher Georges Canguilhem (1989) stated presciently in 1966 that there is something *totalizing* about what is called "the physiological theory" of health and disease, which corresponds to the contemporary holism or systemic view of physiology and systems biology.[35] According to this view, "disease is not somewhere in the man, it is everywhere in him; it is the whole man" (cited in Tutton, 2014, p. 20). While reductionism focused on isolated problems, holism tends to bring *everything* into its remit. This may have both constructive and destructive consequences. However, systems medicine´s use of the term "holism" may from the perspective of humanistic medicine be seen as another appropriation of words and metaphors. First, technologically based genomics appropriated "personalized medicine". Now, systems medicine explicitly does the same with "holism".

Just like "personalization", the concepts of holism, as in "whole person care", integrationism and humanism carry strong positive connotations. As Tutton (2014) makes clear, one of the motivations visionaries of biomedicine may have for using the term "personalized medicine" is to appeal to the self-understanding of the medical establishment and win clinicians over. By appealing to the positive and familiar meaning that lies in caring for whole persons, advocates of systems medicine attempt to win the hearts of general practitioners. This is highlighted by the passage by Vandamme et al. cited in paper II (p. 2). Federoff and Gostin (2009, p. 994) argue in a similar manner in JAMA:

> "Stemming from systems biology, systems medicine incorporates interactions between all components of health and disease. Care for the whole person – derived from the medical tenets of cura personalis – exemplifies the connectivity and integration at multiple levels of systems medicine, expanding medicine beyond reductionism".[36]

[35] In the papers of the thesis I have refrained from using the concepts of "physiological" vs "ontological " theories of health and disease, which are often used in the philosophy of medicine. However, the physiological theory corresponds roughly to important aspects of the holism of systems medicine.

[36] To anchor systems medicine to the foundations of medicine, its advocates explicitly invoke ancient Greece, and the person of Hippocrates. While the systems approach of Hippocrates (involving the clinician "modeling" different aspects of the person) is clearly quite different from today´s computational modeling, Marc W. Kirchner (2016, p. 3) seeks to bolster systems medicine as "genuine medicine" anchored to ancient foundations

However, the redefinition of holism in medicine goes further than just appealing to notions of care for the whole person. It has truly great ramifications. The ancient notion of personalized medicine can be seen as no less than the medical version of the central, humanistic imperative of Western culture: To know the whole person is in an important sense to ”know thyself”. Personalized medicine could be rephrased as ”know-thyself medicine”. Traditionally, this quest towards ”knowing thyself” has been a joint effort between science and humanities (”art” of medicine). With genomic medicine it then started to be actively reconceptualized in reductive, biomedical terms. In the early nineties molecular biologist Walter Gilbert explicitly stated that knowledge of the human genome was the ultimate response to the ancient Greek commandment to ”Know thyself” (cited in Kevles & Hood, 1992, p. 19). Again, systems medicine takes this claim to represent medical humanism further. Systems biologist Enzo Grossi (2010, p. 5) states that the approach favours "a novel humanism directed to the management of the patient as individual subject”. Similarly, according to systems biologist Hans Westerhoff, “Making a precise computer replica of a living cell, and subsequently of the human being itself, is one of the greatest scientific and humanistic challenges” (Westerhoff 2007, p. 150). It is no coincidence that the “quantified self” movement has adopted “Know thyself” as a slogan (Wolf, 2009) or that Leroy Hood´s new P4SM start-up Arivale calls on you to “Know yourself. Take control” (Arivale, 2015a; 2015b). Although systems biologists may acknowledge that these are bold statements made to generate enthusiasm and support, what is promoted here is still no less than a new medical humanism.

Again, nobody has ownership to the concept of humanism, and science is certainly a key part of Western humanism, but surely this represents a significant development for the theoretical foundations of medicine. What Marcum (2008) and others have described as “humanistic medicine” may be left without ownership to the concept of “humanism”. In order to keep track of all elements, computer modeling is a *sine qua non* of systems biology. Computer

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in this way: “Systems medicine and Systems Biology have the same underlying theoretical principle in systems-based thinking – a methodology to understand complexity that can be traced back to ancient Greece.” Similarly, Roncada et al. (2014) use a narrative including Hippocrates and Greek mythology to promote their systems medical “One Health Initiative”: “Starting from Hippocrates, at the Age of Pericles, the One Health Initiative takes inspiration from the Greek father of medicine and is based on his approach which recognizes that human health, animal health and environmental health are part of a whole body. Chiron, the wisest of all centaurs, is the classical mythological representation of an integrated view between man and the environment. Thus, he is the tangible example of the Hippocratic dyad where healthcare is achieved by the integration of man with nature. As a mythological Chiron in modern systems medicine, the integrated body of evidence in proteomics investigations is providing key molecular and analytical knowledge to achieve an evidence based approach”.

algorithms have of course also been employed previously in medicine, for example for cardiovascular risk calculation. However, systems medicine´s vision would, if realized, make the previous role of computers seem insignificant. Perhaps the most dramatic change inherent in the new holism and humanism is this: It is no longer the doctor, a trained human being, who will perform the integration to know the person and personalize medicine; it is a computer. The doctor-patient relationship is sought replaced – at least to the extent that it is practically feasible and desirable for the agents defining systems medicine – by a computational interface, a computer-patient relationship. Systems medicine aims to "creatively destroy"[37] the clinical core of traditional medical generalism and humanism. We are entering an age of *computational personalized medicine, computational holism and computational humanism*. It is essentially the computerization and mathematization of the humane art of medicine. It is art transformed by science.

As the algorithms involved in the modeling and prediction of medicine will grow ever more complex, there is also a very real risk of the research behind medical action becoming less transparent – both for clinicians and for patients. The person defining the basis of action – the new, leading expert of healthcare – will be the programmer of the algorithm, the modeller of the biological system.

The question now becomes, "how much can this 'novel humanism' really know about persons"? I argue (and elaborate below) that there will be limits to its knowledge. Essentially this has to do with the difference between man and machine, and what a machine can know about humans. Systems medicine will not be more holistic than the picture a computer generates of us.

8.4. The New Mirage of Health? Problems of integration, prediction and control

"Medical statemanship cannot thrive only on scientific knowledge, because exact science cannot encompass all the human factors involved in health and in disease"

- René Dubos, The Mirage of Health (1959, p. 260).

[37] Creative destruction is a term coined by economist Joseph Schumpeter to denote a radical, technologically driven systems change. The term was also used by Eric Topol to describe the promised revolution in personalized medicine (Topol, 2012).

In his recent book "*The Digital Doctor*" (2015), hospital physician Robert Wachter has a chapter in which he takes on a question that is central to the promise of systems medicine and this thesis: "*Can computers replace the physician's brain*?"

To Wachter, the question is mostly *who will be best at diagnosis as in recognizing diseases*. That is, he has a *disease focus*. Disease diagnosis is the core of medicine for him. In Wachter´s book (chapter 10), general practice is also described as a place characterized by low complexity and mainly routine work, so he thinks this is where computers will take over most tasks. However, the complexity and messiness of primary care medicine is arguably greater than in more reductive specialist practice. I want to stress that, from a primary care physician's viewpoint, recognizing complex disease patterns and remembering the corresponding treatment is, although absolutely central, perhaps not at the very heart of the endeavor. Instead, general practice is very much directed at helping whole persons attain a level of functioning or health that is meaningful to them, to help them (within limits) achieve their goals and purposes (Cassell, 2013). This is the essence of holistic person-centered care, as opposed to reductive disease-focused care. So, the complexity in question – when we ask if computers can outsmart doctors' brains *in primary care* – is not only about recognizing disease patterns, but about the even more complex and enigmatic concept of *health* (Gadamer, 1996). While disease categories are (sometimes successful) attempts at reducing health problems to discrete, actionable entities, health is irreducibly context-dependent. Besides: It is not necessarily safe to assume that disease can in general be meaningfully categorized into discrete categories that computers, or doctors for that matter, can readily recognize as distinct phenomena through an algorithm. In fact, the systems biological view is fundamentally of health and disease as a continuum and different disease not as distinct, but fluid, interlinked and overlapping phenomena (Bousquet et al., 2011; Hood & Flores, 2012; Sturmberg et al., 2016). A systems view of disease and health actually seems to highlight the challenges for computers and systems medicine.

Already in his seminal book "*The Mirage of Health*" (1959), biologist René Dubos argued from an ecological systems perspective that freedom from disease is incompatible with the process of living and that complete well-being for everyone represents a utopia: Dubos' argument was basically that health means adaptation to an ever-changing environment, including an extremely complex social environment with ever-changing goals and norms. Crucially, Dubos explains, the history of the individual is also an important part of the context

that determines how an event will affect health. And, to make matters even worse, the behavior of human organisms is driven by goals and a desire for change that adds another layer of complexity to the situation. Diseases, or health problems, are inescapable manifestations of these circumstances there will always be new ones; there will be no ultimate satisfaction. And for the purpose of preventive medicine: As "natural situations are so complex that no experimental study can ever encompass and reproduce all the relevant factors", disease is also to a considerable degree *unpredictable*, according to Dubos (1959).

In stark contrast to Dubos, the main clinical, practical promise of P4SM is that its holism, its counteracting of fragmentation, will lead to *a revolution* in predictive and preventive medicine that will lead to better health and economic benefits.

The question about the success of P4SM can be rephrased as follows: Can the visionaries of P4SM prove Dubos wrong?

In this thesis, I argue that P4SM faces serious challenges – or more precisely *uncertainties* – in making its bold promise. These challenges involve problems of integration, predictability and controllability of human beings as complex systems. As these problems are central to my criticism of P4SM, they need some elaboration.

It is of course impossible to know exactly how far P4SM will come in integrating big data on human organisms to predict and control their fate. There is no use pretending that I can know this, or that this Phd has the scope to tackle all questions involved. However, I need to stress that the current thesis is not directed at being *certain* as to what will come to pass; it is to *critically evaluate P4SM as a proposed framework*, *as a vision*, and *the certainty of its promises*. There is also growing skepticism as to the realism of the promised personalized medicine revolution more generally (see e.g. Bayer & Galea, 2015; Caufield, 2015; Diamandis, 2015; Khoury & Galea, 2016; Sørensen, 2016).

To deepen my argument, I will in the following discussion draw largely on criticisms against the promises of P4SM coming *from within* systems biology and medicine. I see such internal criticism as fundamentally relevant. In essence, it shows that – in one sense – systems biology and medicine speak with "two voices": One that loudly proclaims bold promises, and another more cautious voice that speaks of the momentous challenges it faces. While main proponents of P4SM like Leroy Hood may insist that health may be quantified and predicted, others show

more humility. Quote Noble: “On the one hand, it seems sensible to deal only with what we can observe, measure and understand. This is the pragmatic approach of science. (…) On the other hand, it is laughably presumptuous to suppose that this resolves all questions about life. Clearly, it can’t” (Noble et al., 2012, p. 120). Throughout this section, I will highlight the tension between these different voices, and then ask: Why this discrepancy? This question has implications for my further interpretation of how to read its promises.

8.4.1 Incalculability and unpredictability

Firstly, while systems medicine is associated with bold promises of measuring or quantifying life and health (Boogerd et al., 2007 eds, Hood, 2013), it is not at all clear that everything that is relevant for understanding or predicting health can be measured.

Let me begin the survey of the two voices of systems medicine by quoting physician Eric Topol, otherwise a main advocate of personalized medicine and a “creative”, technologically based disruption of professional work:

> "Whatever digital tools are used to simulate and understand a human being, we will never fully replicate the individual, the person. The virtual human is not a real human. (...) No matter how comprehensively, deeply, and finely humans can be digitalised, the human factor and each person´s complexities cannot ever be fully captured; there is an intrinsic and critical chasm with reality full stop" (Topol, 2012 p. 240).

What is striking about this passage is that in Topol´s book, “*The Creative Destruction of Medicine*”, it stands alone, in stark contrast from the rest of the optimistic content. It is as though it has been added by another mind as a kind of humanistic disclaimer, but without Topol considering its possible implications for the rest of his argument: If there is such a *critical chasm* between the person and the digitized model of the person *what does that mean for actually understanding, predicting and controlling the health and disease-states of that person*? It is not that I expect Topol to actually believe that persons, health and disease can be fully controlled, but Topol does not pursue this question judiciously; he just moves on to describe the coming revolution.

In the last years, biology has come to fully realize that most traits, health and disease are complex phenomena influenced by a high number of genes and other “omics” factors, each with a small effect and predictive value. The prospect of integrating so many factors, each

potentially associated with an effect too small to be detectable in isolation, has led critics *within genetics* to conclude that the goal of a transformative, technologically driven personalized, predictive and preventive medicine, which "needs a holistic understanding of each individual patient's unique -omics read-out, is most likely unattainable – for the vast majority of complex traits" (Nebert & Zhang, 2012, p. 910).

Still, mainstream systems medicine retains the dream of predicting the traits of the whole. They also maintain the epistemologically reductionist belief that the whole can be predicted "bottom-up," by quantifying the interactions of molecules in networks (see overviews and criticisms of such views in De Backer et al., 2010; Mesarovic & Sreenath, 2005; Saetzler et al. 2011). New technologies for generating big data combined with new computational power have strengthened a "data mining" philosophy in biomedicine, which is associated with bioinformatics, machine learning techniques and artificial intelligence (Duffy, 2016). However, within systems biology there are strong arguments that such techniques that decipher big data "blindly" without theoretical guidance, will likely not suffice (Noble, 2006). Machine learning may detect bodily patterns that lead to refined risk stratification of patient groups, but also to increasing fragmentation. According to systems biologist Olaf Wolkenhauer, the question of how the fragmented patterns actually connect with each other and to the whole will resurface (Wolkenhauer, 2014). As explained by Noble, the idea of "blindly" computing the behavior of the whole from information on the genomic and other molecular interactions also runs into an intractable *combinatorial explosion* (Noble, 2011). The number of possible mechanistic interactions between 25.000 genes (or proteins encoded by genes) is beyond what computers can perform. This is even so for a just 100 genes. Quote Noble (2011, p. 7), "Even when we reduce the number of genes involved in each function to 25 we still calculate a figure, which is as large as the estimated number of elementary particles in the universe". This explains Noble´s emphasis on knowing the whole by studying the way wholes constrain parts: To know it through the one-sided study of parts is impossible. As Bassingtwaithe et al. (2009) also state, "we would be completely lost within that mountain of data if we did not include the constraints that the cell as a whole exerts on the behavior of its molecules".

Leroy Hood and colleagues also confirm that the amounts of multi-level measurements and interactions represent "a staggering signal-to-noise problem"[38] for predictive medicine, resulting from both technical errors and biological complexity (Tian et al., 2012). Contrary to a blind belief in big data analysis and artificial intelligence, they also opine that, in order to make sense of genomic and other big data, "Domain expertise in biology is essential (…) Without a deep and growing understanding of biological phenomena and networks, it will not be possible to find the critical signals in the tremendous noise generated by vast heterogeneous data" (Flores et al. 2013, p. 5). This emphasis on *biology* in computational biology, and not only *computation*, is a hallmark of systems biology. Key figures within the development of P4SM thus appreciate that there is a need for an integrative and theoretically astute biological approach in which the number of possible interactions is limited by knowledge (models) of how the whole organism is organized, how it constrains its parts through downward causation (Wolkenhauer & Green, 2013).

As another example of the discrepancy between bold promises and more nuanced statements in the systems medicine literature, the "Virtual Physiological Human" is marketed as "a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system". However, the related Digital Patient Project, recognizes – among even bolder promises – that it will remain an essentially fragmented endeavor:

> "At the outset, we point out that the "Digital Patient" will certainly not be a unified, monolithic, all-encompassing mathematical model of the human body from gene to organism. Rather, it will consist of many sorts of models that will be invoked as needed" (Diaz et al., 2013).

A unified, holistic model is promised, and, at the same time, the inevitability of continued fragmentation (in the sense that the model will not be fully unified) is here acknowledged.

Considering the key P4SM promise of prediction of future health states, personal health may in many instances be *impossible* to predict (and thus control). Systems biologists Wolkenhauer and Mesarovic even draw of Zadeh´s *uncertainty principle* to describe a biological uncertainty principle as the biggest problem facing any approach to mathematical modeling in the life sciences*:*

[38] In his book, "The Signal and The Noise" (2012), statistician Nate Silver simply states that, "The signal is the truth. The noise is what distracts us from the truth" (p. 16).

> "…as the complexity of a system increases, our ability to make precise and yet significant statements about its behavior diminishes until a threshold is reached beyond which precision and significance (or relevance) become almost exclusive characteristics. Overly ambitious attempts to build predictive models of cells or subcellular processes are likely to experience the fate of historians and weather forecasters – prediction is difficult, especially if it concerns the future..., and these difficulties are independent of the time, amount of data available or technological resources (e.g. computing power) thrown at the problem" (Wolkenhauer et al., 2003).

At the same time, often cautious and thoughtful theorists, like Wolkenhauer and Noble for example, will join other authors promising a transformation in disease prediction and prevention through P4 medicine through integration of a cloud of *billions* of data-points per person (Bousquet et al., 2011). The writings of systems biologist Stuart Kauffman gives a very clear example: On the one hand, he has argued that the creativity and emergence of the universe entails unpredictability:

> "Science itself is more limited by the un-prestatable, unpredictable creativity in the universe than we have realized, and, in any case, science is not the only path to knowledge and understanding. Science cannot explain the intricate, context-dependent, creative, situated aspects of much of human action and invention, or the historicity that embraces and partially defines us. These, however, are just the domains of the humanities, from art and literature to history and law. Truth abides here, too" (Kauffman, 2008a, p. 7).

At the same time, Kauffman supports a P4 medicine built on a belief in the same ability to predict health outcomes in a very complex system:

> "We are entering an era in which we can measure those factors that RCTs[39] have considered dark matter in the information space of patient-specific traits and have randomized away. We can determine the multi-causality network of each individual patient. The arrival of the 'omics technologies—genomes, epigenomes, transcriptomes, proteomes and metabolomes—is about to shine light into this dark matter of patient-specific causality. This offers an opportunity to unite the "unscientific," but patient-focused alternative medicine with the "scientific," evidenced-based best practices, or one-size-fits-all medicine" (Kauffman et al., 2014, p. 31).

I am not saying that any of the two statements is either true or false. It is of course valid to state in one context that the emergence of complex systems is radically creative and unpredictable, and in another emphasize what we *can* predict. However, the tones in the two papers, each written by Kauffman, are very different. It is striking that the voice emphasizing unpredictability in the first paper does not join the chorus when the vision of P4SM is conjured in the second.

[39] Randomized controlled trials.

Even Leroy Hood, the prime maker of bold promises in systems medicine, will sometimes accept the serious challenges involved. A committee outlining the role of theory in 21st Century Biology, which includes Hood, states that,

> "In physical systems, some processes are intrinsically unpredictable because they involve features that can only be described in probabilistic terms. Other systems are unpredictable even though they are completely deterministic, because of their chaotic dynamics and extreme sensitivity to initial conditions. For some physical systems, attempts to predict fail simply because the important controlling details of the components are not well understood. Most current biological modeling implicitly assumes that accurate predictions can be made once sufficient information about the biological system is available. However, it is possible that some biological processes will be intrinsically unpredictable because of principles analogous to chaos or quantum indeterminism".

As another striking example, leading systems biologist Westerhoff and colleagues have made the argument that the emergence of wholes can be reconstructed from the knowledge of component properties (Kolodkin et al., 2013). On the other hand, Westerhoff and Kell (2007, p. 64) state that,

> "Of course there are some exceptions with respect to a straightforward calculation of all aspects of life. These include deterministic chaos, systems that are extremely heterogeneous, and life beyond its simplest form already present on unicellular microorganisms".

The elephant in the room: The human body *is* precisely an extremely complex and heterogeneous system beyond life at its simplest form. As physicist W. J. Firth noted in a BMJ paper (that coincided with the beginning of the Human Genome Project), complexity theory, nonlinear dynamics or *chaos theory*, predicts that it will in many instances be hard to forecast who will get diseases, or who will respond to which treatments, not because of incomplete knowledge about each person, but because the system in question is inherently unpredictable (see also Smith, 2011):[40]

> "It follows that we patients should not expect too much of our doctors! (…) Prediction is not trivial or easy. In fact, chaos theory (…) has shown us that predictability is the exception rather than the rule, even for what seem like simple physical systems. A human being is immeasurably more complex than any demonstrably chaotic system – the question can be turned around: How can anything be predicted about a person?" (Firth, 1991, p. 1565).

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[40] In his thesis "Bad luck and the tragedy of modern medicine" (2005), medical doctor and philosopher Ståle Fredriksen, argues that whether or not one acquires disease must to a considerable degree be understood in terms of good or bad luck.

I will turn to the latter point Firth makes in the next subsection, human biocomplexity, but first it should be mentioned that even if the P4 approach worked perfectly, it would still take years, even decades, of observational time to establish this fact in terms of the hard end-points of mortality and morbidity. In the meantime, we are facing an age of "big noise" where we have to constantly pay attention to, but do not really know what to make of, all the data that are still unyieldingly churned out of "omics" technologies. While the vision of P4SM will have us believe that we are heading towards a revolution in clinical utility, we may just as well be heading for "big uselessness" and a "Digital Wild West" in which companies provide services laced with great promises, but no evidential core (see e.g. the P4SM company Arivale, 2015a; 2015b as a prime example).

8.4.2 Human biocomplexity

As this thesis is finalized, the election of Donald Trump as President of the USA is a fresh memory. One of the most striking aspects of the election was how the predictive models of pollsters were misleading and failed to foresee the winner. Likely, this was an example of how it is hard to incorporate the complexity and creativity of humans and human culture in predictive models. Nate Silver, statistician and influential leader of the website www.fivethirtyeight.com also failed, but in his book (2012), he illuminates why we often fail to predict correctly:

> "The most calamitous failures of prediction usually have a lot in common. We focus on those signals that tell a story about the world as we would like it to be, not how it really is. We ignore the risks that are hardest to measure, even when they pose the greatest threats to our well-being. We make approximations and assumptions about the world that are much cruder than we realize. We abhor uncertainty, even when it is an irreducible part of the problem we are trying to solve" (Silver, 2012, p. 19).

Besides the uncertainty inherent in handling complex systems, it is the real-world biological complexity of the human organism that defines the challenges to scientific explanation, integration and prediction in P4SM (Strand et al., 2004). At the end of the Human Genome Project one of its pioneers, John Sulston, stated that, "the ultimate aim of biology is to compute an organism from its genes (being mindful of the role of the environment and random factors in development)" (Sulston & Ferry, 2002, p. 272). The pursuit of this goal has now materialized as systems biology and medicine. Sulston interestingly also predicted that

the fulfilment of this goal would depend on a computer, or computer model, that would be a brain in its own right, a form of *artificial intelligence*. Considering the humanistic commandment to "know thyself", a computational model based on intense "participatory" self-monitoring may be regarded as a very advanced "selfie", a technologically based picture. The individual person, the self, represents the human complexity the model tries to capture.

It is here that systems medicine runs into the most profound challenges and questions. It is very literally faced with the complexity of human beings, including conscious experience, goal-directedness, creativity, etc. Interestingly, systems medicine is beginning to explicitly acknowledge this: As systems biologist Jesse Fox tells New Scientist (Geddes, 2014): "If you're going to model the physical body, you really need to think about modeling a person's psychological state as well".

The question then becomes: What biocomplexity is not buried in the term "psychological state" of humans? It is not as if these questions are lost on systems biologists (see e.g. Noble, 2006). Systems medicine is associated with profound philosophical discussions and clear calls for new theory and new mathematical principles that can deal with the order and patterns of life (Cornish-Bowden, 2006; 2011; Gjuvsland et al., 2013; Noble, 2010; Omholt 2002; 2013). There exists an acknowledgement that tools from engineering and physics will not do. As one theorist points out, "the conceptual revolution required to account for life will also require a new mathematics" (Gare, 2013, p. 12, see also e.g. Noble, 2006; Boogerd et al., 2007 eds.). Sometimes, these calls are made with reference to theoretical biologist Robert Rosen, who strongly opposed the machine metaphor of life, and argued that its tacit premise dulled biological thinking: "The question 'What is life?' is not often asked in biology, precisely because the machine metaphor already answers it: 'Life is a machine'" (Rosen, 1991, p. 23).

However, the biggest conceptual problem for mainstream systems medicine today may still be that it continues to (tacitly) conceptualize living human beings *as though they were machines* (Letelier et al., 2011; Rosen, 1991). It is still strongly focused on the level of molecular parts, risking further molecularization of our view of the human organism (De Backer et al., 2010; Lock, 2013; Niewöhner, 2011). Still lacking a mathematics or theory that truly does justice to its area of study (life), systems biology models organisms as more complex machines than previous biology, but still in engineering terms (Galas et al., 2008; Hood & Flores, 2012; Keller, 2007; Lazebnik, 2002). However, these models may simply not be sufficient for

understanding humans (McGuire et al., 2013; Ziegelstein, 2015). Systems biology or systems neuroscience (De Schutter, 2008) cannot currently model a human brain or the way a person adapts to a complex environment and how the brain mechanistically constrains the other organs, cells and molecules of the body through, for example, neural and hormonal concomitants (Danese & McEwen, 2011; Pavlov & Tracey, 2015). Crucially, human biocomplexity is such that people may not find it meaningful or possible to respond to risk estimates and participate in the disease-preventing endeavor with the needed "participatory" behavior (Hollands et al., 2016; Knoblauch, 2014; Linster, 2011).

Biologist Bernd Rosslenbroich recently published an innovative paper aimed at enhancing medicine´s conceptualization of the organism, acknowledging that this is especially important for understanding "the person" in personalized medicine. Of special interest to this discussion, he refers specifically to paper I of my thesis:

> "Vogt et al. [167] state that integrative systems biology can contribute to rehabilitating "the person" in human biology, thus building a much more adequate background for humanistic medicine. They conclude, however, that it still does not integrate central qualities of a person such as consciousness, meaning and value. This is correct, as integrative systems biology only attempts to come to a more coherent notion of the living organism (the level of "being alive"), identifying the instrument for psychical and cognitive abilities in humans (Rosslenbroich, 2016, p. 28)".

The point that systems biology is "only" attempting a fuller understanding of life is much appreciated. However, I would like to note that it is unclear if one can have a fully "coherent notion" of the living organism – let alone persons and of health for personalized medicine – while omitting phenomena of the "mind" like consciousness, meaning and value. In a book that, in my view, represents science´s cutting edge in conceptualizing life, biological anthropologist Terrence Deacon states that,

> "…despite the obvious and unquestioned role played by functions, purposes, meanings, and values in the organization of our bodies and minds, and in the changes taking place in the world around us, our scientific theories still have to officially deny them anything but a sort of heuristic legitimacy. (…) In the process, it has also alienated the world of scientific knowledge from the world of human experience and values. If the most fundamental features of human experience are considered somehow illusory and irrelevant to the physical goings-on of the world, then we, along with our aspirations and values, are effectively rendered unreal as well" (Deacon, 2012, p. 12).

The fundamental problem facing personalized systems medicine is that the challenge outlined by Deacon will not go away. A main part of my argument is that this has profound

implications for our reasons to believe the promises of systems medicine. One may of course argue that the fact that we cannot model everything does not preclude significant improvement. That is true, but the promises of "holistic", personalized systems medicine are wide-ranging. To the extent that a true holism is in fact needed to understand human health and disease, I think these caveats should be part of the promissory picture.

8.5 A game of expectations: Systems medicine as a scientific dream

"*This magic day when super-science mingles with the bright stuff of dreams*".
– Rush, "Countdown" (1984)

The idea of a genomically based personalized medicine has been associated with bold promises from the beginning. The most eloquent maker of such promises is perhaps biologist Leroy Hood – who was as seminal to the Human Genome Project in the early 1990s as he is to systems medicine today. Already in 1992, Hood stated that gene sequencing would enable medicine to "move from a reactive mode (curing patients already sick) to a preventive mode (keeping people healthy)" (Hood, 1992, pp. 156 and 158; see also Collins & McKusick, 2001; Gilbert, 1992). In an early lecture, Hood also stated that, "My prediction is that preventive medicine will extend the average lifespan by 10-30 years" (Hood, 2002). Individuals knowing their own risk-estimates would be empowered to take control over their own health (an aspect of what is today called *participatory medicine*). Already in 1992, Hood declared that knowledge of DNA would lead to a *revolution*: "I believe that we will learn more about human development and pathology in the next twenty-five years than we have in the past two thousand" (Hood, 1992, p. 163). As a recent Hood biography reveals, Hood – who in many ways personifies the drive towards personalized medicine and systems medicine – has made this statement, with slightly different wording, several times in different settings (Timmerman, 2016). However, 25 years have now passed, and it is safe to say that the claim that we have learnt more from 1992-2017 than up until 1992 is highly controversial (Joyner et al. 2016).

Propositions about what biology will achieve in the future are in general made about a point that is conveniently beyond critical scrutiny, say "in 5, 10 or 20 years' time" (see e.g. Flores et al., 2013; Hood et al., 2015). The revolution is always "*not now", but "soon*"[41].

Both in the papers of this thesis and in the above discussion, I argue that there is a significant discrepancy between what empirical evidence and philosophical considerations suggest is realistic and the published, far-reaching promises of P4SM as a holistic and highly potent form of personalized medicine that will *revolutionize* the utility of preventive medicine.

In this section I will address some questions that arise when discrepancies between promises and what is realistic have been identified: Why the discrepancy between cautious and bold statements in systems medicine? Why is systems medicine portrayed as "holistic" when it cannot fully account for human wholes? Why do the visionaries conceptualize the body, health and disease in terms of complex systems or wholes, but yet as predictable and controllable when human wholes may often be unpredictable and uncontrollable? Why are expectations created about a revolution in preventive medicine when there is considerable uncertainty attached to these predictions? As my co-supervisor Irene Hetlevik, who has worked with potentials and pitfalls of cardiovascular prevention for many years (Hetlevik, 1999), asked at one point when I presented my work:

> "I am ever more taken aback by the way people within biomedicine and academic medicine allow themselves – and are allowed to – sell in promises of the future of medicine that put them in a position to build their empires on loose foundations" (Hetlevik, personal communication).[42]

Towards the end of this project, at one of the academic gatherings I attended on systems medicine,[43] I asked one of its proponents, pediatric oncologist Angelika Eggert, this question. I found the simple answer striking:

> "Yes, people have been making strong claims and promises. But it is also necessary to make these promises. You will get no funding if you tell politicians that 'we do not really know' or if you are really self-critical. I agree that we should not give false promises, but

[41] This expression, "not now, but soon!" used about biomedical promises was coined by the Think Tank at the General Practice Research Unit at NTNU (see Acknowledgements).

[42] Irene Hetlevik has also spearheaded work on scientific responsibility and demands that researchers consider downstream consequences of their work (see Forssén et al., 2010).

[43] Interdisciplinary Winter School on "Integration and Translation in Systems Medicine" Universität Hamburg, February 1-5, 2016.

> we should also not underplay a field that I think has great promise. It is a game of expectations" (Eggert, 2016, personal communication).

In the following part of my discussion I will elaborate on the question above, and the *game of expectations* referred to.

8.5.1 Is the promise of a revolution in clinical utility a straw man?

However, first I would like to address an important question. When I state that the main clinical, practical promise of systems medicine is a revolution in clinical utility, especially in preventive medicine, is this straw man argumentation? A straw man is the act of making it a premise that your opponent argues or proposes something, which he/she does in fact not, and then argue against that invented position.

In one sense it may be. Not everyone involved in systems biology and systems medicine is making this bold promise explicitly, and not everyone who does, does it without more cautious statements attached. However, I do think it is fair to state that the promise is *a revolution* in clinical utility.

In my primary material the word "revolution" appears quite frequently. It is used to denote general technological and scientific developments in biomedicine (Aggarwal & Lee, 2003; Alyass et al., 2015; Ehrenberg et al., 2003; Kohl & Noble, 2009; Li-Pook-Than & Snyder, 2013; Younesi & Hofmann-Apitius, 2013; Weston & Hood, 2004; Zhang et al., 2013), our future ability to develop new drugs (Kitano, 2002a; Penrod et al., 2011), a methodological and conceptual revolution (Bizzarri, 2013; Noble, 2010), diagnosis and cure. It is also specifically used to characterize promised changes in diagnosis, cure and preventive medicine (Agusti et al., 2010; Flores et al., 2013; Galas & Hood, 2009; Geddes, 2014; Grossi, 2010; Hood & Galas, 2008; Hood & Flores, 2012; Hood et al., 2012; Hunter et al., 2013; Karr et al., 2012; Loscalzo & Barabasi, 2011; Regierer et al., 2013; Smarr, 2012; Tian et al., 2012; Wolkenhauer et al., 2013). In a typical way, Wang et al. (2015, p. 156) close their visionary proposal by stating that,

> "Although systems medicine is in its early stages and faces many challenges, it will no doubt revolutionize the practice of medicine and healthcare".

The even stronger term ”paradigm shift” or ”paradigm change” is also regularly used by theorists and visionaries of systems medicine. Again it is used to denote a general trend in biology and medicine (Aggarwal & Lee, 2003; Ideker et al., 2001), a conceptual development (Boissel et al., 2015; Goldman et al., 2015; Gomez-Cabrero et al., 2014; Okser et al., 2013; Voy, 2011; Westerhoff & Palsson, 2004), but also the clinical utility of medicine more generally and preventive medicine in particular (Capobianco, 2012; Diaz et al., 2013; Duffy, 2016; Grossi, 2010; Hood et al., 2012; 2013; 2015; Kirschner et al., 2013; Smarr, 2012; Younesi & Hofmann-Apitius, 2013).

These statements are not only made by individual authors, but by groups of authors who are defining to the thrust of medicine. Recently, Hood et al. (2012, p. 1) explicitly state about P4 medicine that, ”This reflects a paradigm change in how medicine will be practiced that is revolutionary rather than evolutionary”.[44] A roadmap towards systems medicine developed by a large group of leading figures and sponsored by the European Commision, states that, ”In essence, Systems Medicine aims at introducing a paradigm shift where physicians substitute the current reactive medical practice by a prospective 4P medicine” (Kirschner et al., 2013, p. 5). Another large group of authors similarly promise that, ”P4 medicine represents by itself a revolution that extends far beyond what is usually covered by the term personalized medicine” (Bousquet et al., 2014, p. 4).

As a last example, the authors of the Digital Patient Roadmap, state that...

> ”However, a new paradigm shift is about to occur: personalised medicine promises to revolutionise the practice of medicine, transform the global healthcare industry, and ultimately lead to longer and healthier lives. The Digital Patient is part of this new paradigm, grounded on the principle that it is possible to produce predictive, patient-specific mathematical models for personalised healthcare” (Diaz et al., 2013, p. 39).

I think this documents that it is not only straw man argumentation to make it a premise for this thesis that a revolution in clinical utility is a promise of P4SM. However, it may also perhaps be stated that although I am not inventing this straw man, the promises of systems medicine may in one sense be seen as ”straw men” that its visionaries invent themselves: In order to realize their goals, they invent a version of the future that may easily be put to the torch.

[44] Hood repeatedly uses words like “revolution” or “paradigm” in his keynote lectures and publications. Searching my material, I find that Hood has used the phrase ”revolution” in 29 publications since 2002, with the word ”paradigm” being used in 20 publications.

8.5.2 The stakes of systems medicine

In understanding this and Eggert´s reference to a *game of expectations*, I think it is useful first to consider the stakes involved in personalized systems medicine. These stakes are hard to overstate.

As systems biologist Stig Omholt has noted, ”The dream of understanding the causal basis of biological forms has been with us since Aristotle” (Omholt, 2002). Personalized (or precision) medicine does in many ways represent the spearhead of modernity and its core project of understanding and taming nature, including human nature. This project may be exemplified by the statements of biologist Jacques Loeb (1859-1924), a pioneer of the engineering mindset in biology which pervades systems biology today, and Claude Bernard, hailed as a key figure in the establishment of scientific medicine and as the “first systems biologist” (Noble, 2007). Loeb stated that…

> “It is possible to get the life-phenomenon under our control (…) such a control and nothing else is the aim of biology” (cited in Pauly, 1987, p. 174).

Bernard states about the workings of the body that,

> “When an experimenter succeeds in learning the necessary conditions (…) he is, in some sense, its master; he can predict its course and appearance, he can promote or prevent it at will” (cited in Comfort, 2012, chapter 2).

Systems medicine is the modern continuation of Loeb´s and Bernard´s dream: It represents science´s uttermost and most publicized attempts at gaining (beneficial) control over human biology and continue to transform our lives through technology. Not only the prestige[45] of science is at stake: Large amounts of money and considerable political prestige have already been invested in the idea. And not least, embedded in the project of personalized medicine lies much of the hope that, in the future, we may be able to handle some very real and devastating health issues. The failure of personalized medicine would thus in many ways entail a major failure of the whole project of modernity. The promises of gene-centric, DNA-based personalized medicine have, as one editorial in Nature Biotechnology (Editorial, 2012, p. 1) puts it, translated into ”a rather pedestrian form of progress in personalized care rather

[45] It seems relevant to note that the word ”prestige” originally had a meaning that is now found in the practice of an illusionist, that of pulling a ”magic” trick. According to the oxforddictionaries.com, its origin is Latin praestigium, meaning ‘illusion’, or praestigiae (plural) ‘conjuring tricks’. The transference to today´s meaning (as in the Nobel Prize being a ”prestigious” award) occurred by way of the sense ‘dazzling influence, glamour’, at first depreciatory.

than a march to the future". Such disappointments have been observed to, "have resulted in lasting damage to the credibility of industry, professional groups and investment markets. That is, until the next promise arrives!" (Borup et al., 2006)

So, when the promises of genomic personalized medicine is perceived as failing, it is perhaps not strange that a new set of promises arises in the form of systems medicine to represent a new horizon of biomedicine and modernity. There is reason to think that the theorizing and vision making of systems medicine perform functions that are other than "traditional" scientific truth seeking. In cementing these realizations in my thinking about systems medicine, I am indebted to sociologist Richard Tutton (2012; 2014), whose work introduced me to a literature in science studies and sociology that explicitly studies the creation of promises, dreams of the future and expectations, *a sociology of expectations* or *sociology of the future* (Borup et al., 2006; Hedgecoe, 2004; Selin, 2008). Such academic studies focus precisely on the kind of publications that comprise my primary material: Reviews, perspective articles and opinion articles, highlighting the way expectations are generated to guide and support technoscientific endeavors. As science studies scholar Kaushik Sunder Rajan argues, genomics and biotechnology is a game that is "constantly played in the future in order to generate the present that enables that future" (Rajan, 2006, p. 34): The game of expectations.

8.5.3 Systems medicine as promissory science and venture science

Sociologist Adam Hedgecoe has introduced the concept "promissory science", a science that "exists more in the speculations and promises of its supporters than in terms of scientific results and marketable products" (Hedgecoe, 2004, p. 17). Systems medicine can, I think, fruitfully be regarded as such a promissory science, the heir to the genomics and personalized medicine that Hedgecoe, Rajan and Tutton have already described (Hedgecoe, 2004; Rajan, 2006; Tutton, 2012; 2014).

Another relevant concept is "venture science", which signifies a form of technologically based science that is merged with venture capitalism. According to Tutton, "venture science' is promissory, risky and defined by visions and hype. To generate value in the present in the name of realizing a promised future, venture science sells a vision even if – as is often the

case – this is never materialized as sold" (Tutton, 2014, p. 5). As highlighted by Rajan and Tutton, personalized medicine has come to encapsulate the idea of a venture science:

> "'Venture scientists' of the late twentieth and early twenty-first century have embraced personalized medicine, aiming to realize economic value from the science of genomics and its application to medical research and practice. In this context, personalized medicine also encapsulates both the excesses of promissory science and the inevitable disappointments and disputes that follow" (Tutton, 2014, p. 3).

In venture science, which merges speculation and innovation, visions of the future often take the form of *hype* (Rajan, 2006). And, as Rajan states, "Hype is not about truth or falsity; rather, it is about credibility or incredibility" (Rajan, 2006, p. 114). For a modern biomedical vision like systems medicine to be realized it may be *credibility* rather than *truth* or *realism* that is the viable currency: Too heavily laden with realism and truth, the bandwagon may not even get on the tracks, let alone make it to far-off destinations. For something to be "credible" is to be "*able to be believed; convincing*"[46]. The discipline concerned with convincing people is *rhetoric*, in which *logic* or *critical thinking* (the soundness and strength of the argument itself) is only one ingredient (see method section). I have to admit I have spent much of my Phd project studying the publications outlining systems medicine as if they were aiming at realism, truth and logical arguments only, and not as if they were about *credibility*. I have to a certain extent developed a critique of something that was never meant to be *true*, but just convincing. Systems biologists may shake their heads at my project, asking themselves "did he really take it seriously?". Wanting to analyze philosophy and facts and ending up in a game of expectations does feel somewhat dissatisfying. However, this is also the purpose of critical thinking: To separate logical, well-grounded arguments from other forms of rhetoric and spin. I hope there is some merit to taking the theories and promises of systems medicine at face value, if anything to challenge the makers of scientific visions to engage in more judicious discussions, which take the potential downsides of their creations more seriously.

8.5.4 Systems medicine and the "biomedical imagination"

To follow up on the above considerations: Why is the human body portrayed as predictable and controllable in systems medicine?

[46] See oxforddictionaries.com

As I mentioned in my Rationale section, medical professionals (including medical scientists) "live" in part, quote Perkin (1989), "by persuasion and propaganda, by claiming that their particular service is indispensable to the client or employer and to society and the state". The very way professionals develop their theoretical basis – including its visions and promises of the future – may be guided by professional requirements other than truth and doing good. Crucially, medical scientists are allowed to shape their own view of the human being or organism, using their metaphors and models according to their requirements and needs.

Two additional concepts that are highly useful in further discussing systems medicine along these lines are ideas of *the biomedical imagination* and a (future) *biomedical imaginary*. According to sociologist Catherine Waldby, the "biomedical imagination" is "…biomedicine´s speculative universe, it is a way of proposing relationships and processes, of imagining the world according to its own requirements" (cited by Tutton, 2014, p. 7). What the biomedical imagination creates is called the "biomedical imaginary":

> "The biomedical imaginary refers to the speculative, propositional fabric of medical thought, the generally disavowed dream work performed by biomedical theory and innovation. It is a kind of speculative thought, which supplements the more strictly systematic, properly scientific, thought of medicine, its deductive strategies and empirical epistemologies. While medicine, like all sciences, bases its claims to technical precision on strict referentiality, a truth derived from the givenness of the object, the biomedical imaginary describes those aspects of medical ideas which derive their impetus from the fictitious, the connotative and desire" (Waldby, 2000, p. 136).

Relatedly, Waldby describes what she calls *iatrogenic desire*. Doctors may be familiar with the concept of "iatrogenic harm", which acknowledges that bodies are shaped by complex and unruly causal effects and may be damaged from medicine´s touch. "*Iatrogenic desire*" refers to the way biomedicine conceptually creates bodies according to its needs, that is…

> "…kinds of bodies which are stable, self-identical entities rather than fields of perverse contingency. It is a product of (…) a desire for living bodies, which (…) comply with medicine´s fantasies of perfect management (Waldby, 2000, p. 113).

Such an "iatrogenic desire" is very much present in systems medicine. This is why it mostly chooses models from engineering, physics and computer science. This is why its holism still aims at prediction and control. As Waldby points out, the computer has become the new "metatechnology of life": "The claims of future prophylactic developments made on behalf of the Human Genome Project depend on the possibility of producing healthier bodies through the technical manipulations of code, in a stable relationship of technical cause and bodily

effect (Waldby, 2000, p. 113). In computational systems medicine, the biomedical imagination or biomedical imaginary is taken a step further: The computational model becomes the most important tool that limits and inspires how the body may be conceptualized. And it is no longer concerned with only the genome as a program or code of life, but with the interactions between genome and environment, of *the whole body as a computational system*.

In sum, the answer to Hetlevik´s question, and Eggert's "game of expectations" is that theoretical publications in biomedicine serve a dual purpose: The models and concepts they convey are both carriers of biomedical fact and biomedical dream. While empirical, scientific papers may be objectively concerned with the facts about matter and mechanisms, the promissory part of science discourse is based on the very part of human nature that science usually denies the existence of: Its capacity to dream, to continually create a causally guiding image of the future, its goals, purposes, meaning and values, that is, its own *final cause*.

What is confusing, however, to those unaccustomed to science´s *game of expectations*, is that while one expects scientific and philosophical rigor, facts and serious theorizing is hard to tell apart. This leads me to the next point in this discussion: Is there something ethically wrong with promising and overpromising?

8.5.5 Is the systems medicine vision irresponsible?

As I noted in paper II, one does not have to actually succeed in controlling human wholes for holistic medicalization to be realized – with all its potentials and pitfalls: One only needs to believe it possible and make the attempt. The making of theories, visions and promises is vital in establishing the belief that makes us act. An act that makes us act is also subject to ethical judgement.

So, *when is a scientific vision immoral*? This question was posed in an abstract by colleagues at NTNU, Sophia Efstathiou and Rune Nydal, already in 2012 (Efstathiou & Nydal, 2012). At the beginning of my project, I was not ready to focus on its significance. At the end of the project, I can. I would rephrase the question: Is the systems medicine vision scientifically irresponsible?

Although the identification of unrealistic or unsubstantiated promises in systems medicine may at first seem unethical, the matter of whether it is ok to create great goals and expectations is not clear-cut. As Eggert stated in the above citation, "we should also not to underplay a field that I think has great promise". This is a very legitimate concern. The history and sociology of the future, visions and expectations point to important functions played by these "creatures of the future tense" (Selin, 2008; see also Brown & Michael, 2003; Hedgecoe, 2004). They provide justification for social, political support and economic support and provide a common language and agenda uniting disparate disciplines and agents. Overpromising may even be regarded as a necessary evil (Hedgecoe, 2004, p. 180). Expectations and predictions about the future drive research and development; they are "wishful enactments of a desired future" (Borup et al., 2006, p. 286). As Brown and Michael (2003, p. 1) state,

> "Future expectations and promise are crucial to providing the dynamism and momentum upon which so many ventures in science and technology depend. This is especially the case for pre-market applications where practical utility and value has yet to be demonstrated and where investment must sustained".

The creation of expectations may be seen as essential to the project of making scientific progress come to pass, "in both the development of the technology itself and in the shaping of the social, regulatory and economic environment into which the technology will emerge" (Hedgecoe, 2004, p. 27).

We are surrounded by the half-fulfilled dreams of people who did perhaps overpromise, but nonetheless achieved something substantial. Visions are ladders in the mind´s eye. We need those ladders.

Yet, predictions about our common future on this planet should not be too bold, but based on our very best models and knowledge. They should be our very best, educated guesses. A society has always had to guard itself against false prophets. Why? Because misleading predictions inspire the wrong actions, actions that may involve potential harms and squander our resources. Pushing the envelope through rhetoric may also create unwarranted expectations and divert precious resources from other potentially productive activities. Brown & Michael, (2003) note that, "In some cases, the failure of expectations has severely damaged the reputation and credibility of professions, institutions and industry". It has been suggested, given the uncertainties involved,

> "that proponents of personalised medicine and other biotechnologies should make more modest, qualified claims for potential innovations. Expectations that are unrealistic (i.e. not supported by strong evidence) or unaccompanied by appropriate qualifications (for example by acknowledgement of attendant uncertainties, such as the impact of changing markets, or likely limited applications and benefits), are misleading and can adversely affect the health and wellbeing of individuals and communities. (…) Unrealistic expectations may also result in considerable costs to the community as a whole through skewing funding towards innovations that are likely to benefit only certain groups" (Petersen, 2009, p. 5).

Undermining the trust of systems medicine through overpromising may also hit back on systems medicine: "This may mean that future research that has a demonstrably high likelihood of improving people's lives may never gain the level of community support necessary to achieve the commitment of governments and funders" (Petersen, 2009, p. 10).

The ethical implications of visions and expectations have been largely overlooked. I cannot provide a definitive answer as to the irresponsibility of the systems medicine vision as a whole. However, I do think it has important shortcomings that may make it irresponsible at least in some regards. Its use of concepts like "personalized" and "holistic" to sell its vision, while being in fact not personalized or holistic in any traditional sense, is ethically tenuous. In some instances it may be likened to a form of "newspeak" in Orwell's 1984 language – holism is reductionism, personalized is depersonalized, democratization is a new paternalism (Orwell, 1949). In particular, the onesided promotion of P4SM as a liberating force seems disconcerting, as its participatory aspect may also become disempowering (Green et al., 2015; Kappelgaard, 2015; Lupton, 2012; 2014; Prainsack, 2014; Tjora, 2004; Vogt et al., 2014b).

Iona Heath, a leading voice in Britich general practice, cites political theorist Herbert Marcuse, who, in 1964, stated that, "'Totalitarian' is not only a terroristic political coordination of society, but also a non-terroristic economic-technical coordination which operates through the manipulation of needs by vested interests" (Heath, 2013, p. 2). Heath refers to Marcuse in order to describe important aspects of the modern medico-industrial complex, especially of preventive medicine. P4SM has vested interests in the unstated goals of the medical profession (see Rationale, section 4.1). One way to manipulate our needs in order to make us willing participants is by appealing to our craving for certainty and control in life, for no pain, no death and personal freedom (Heath, 2013). With an appeal to holism and democratization (e.g. Hood & Price, 2014a), P4SM risks becoming the epitome of what Heath referred to. In particular, a totalizing medical framework (cf. Downing and Canghuilhem in section 8.3),

which aims at exerting total ("holistic") control of human life, risks slipping into a form of totalitarianism. When P4SM alluringly promises people to "know yourself" and "take control" of their life through intense self-monitoring (Arivale, 2015a; 2015b), this may actually conceal a profound loss of freedom.

Concerning privacy issues the negative prospects are as daunting as they are realistic. To speculate about the future: Our contemporary society is characterized by two major fears or risks (in addition to climate change): terror attacks and the failure of our own bodies. A confluence of these two fears and the technologies we have developed for prediction and control of them may conceivably lead to the ultimate surveillance society. In the future, what may be downloaded from our smart-phones will not be a few data, but a systems medical *avatar* based on big data about your being ("avatar" is actually a metaphor used by the EU Digital Patient project to describe a future virtual mirror image of all of us (Diaz et al., 2013)). A state or company with poor respect for individual freedom that wishes to monitor people, for example with reference to risk of terror, could access such an avatar containing our integrated physiology, sociometrics, psychometrics and environmental exposures.

Crucially, systems medicine's visionary papers very seldom discuss the downsides of medicalization and increasing medical control (see papers II and III). On the whole, the main promise of a "revolution" in preventive medicine that will bring a huge boon to individual and public health, save costs, save welfare states and secure income for future generations, is dubious and therefore ethically questionable. To propose a wholesale revamp of the entire healthcare system without judiciously considering the impact of big data on, for example, overdiagnosis is blatantly unprofessional and irresponsible. It should also be mentioned that results from the Institute of Systems Biology´s "Hundred Person Wellness Project (HPWP)", which was undertaken in 2014, have not yet been published in peer reviewed journals. If this remains the case, it is effectively what professor of health research, John Ioannidis, has called "stealth research" ("ie, research not communicated in the peer-reviewed literature") (Ioannidis, 2016). This brings me to important implications of my work.

8.5.6 Scientific responsibility, journal editing and anti-hype guidelines

The above I think highlights the need for scientific responsibility in systems medicine, the willingness to take responsibility for the downstream effects of not only one´s finished products and research findings, but also for the negative consequences of overpromising and hype (Forssén et al., 2010).

Many of the visionary papers that constitute my material are printed in highly regarded journals. However, while peer-review and editing is designed so as to tightly regulate interpretation of results in empirical papers, opinion pieces, reviews and perspective articles allow scientists to make bold promises without much justification. As the making of visions is important for our action, not only innocent speculation, I suggest that journal editors should demand more of their visionary authors. Although propositions about the future cannot be examined and judged just like our propositions about the present, there must be some form of accountability. As Sara Green and I conclude in paper III, the burden of proof should be placed firmly on the shoulders of those articulating the vision. A guideline containing a simple set of rules or routines for such papers should be put in place, for example demanding that visionaries consider at least known potential risks (e.g. overdiagnosis). For example, the International Society for Stem Cell Research has issued "anti-hype" guidelines that "highlight the responsibility of all groups communicating stem cell science and medicine— scientists, clinicians, industry, science" (Joyner et al., 2016, p. 1).

8.5.7 Prospective, proactive quaternary prevention

Another related, important implication of this thesis is, I think, that it highlights the need for what I will call a vision-focused *prospective, proactive quaternary prevention*. Quaternary prevention, as mentioned in Section 4, refers to increasing efforts in preventing negative effects of medicalization, especially with regard to preventive medicine (Brodersen et al., 2014; Jamoulle, 2015). Incidentally, it has been abbreviated "P4" (primary, secondary and tertiary prevention being P1, P2, P3). P4 medicine is also often labelled as "prospective or proactive" in addition to the other plosives[47]. So, what I am proposing is a prospective,

[47] A plosive denotes "a consonant that is produced by stopping the airflow using the lips, teeth, or palate, followed by a sudden release of air" (see oxforddictionaries.com). I imagine that it is no coincidence that

proactive quaternary prevention directed against a prospective, proactive P4 medicine. A "P4 against P4" studying the theoretical deliberations, visions, expectations and promises of cutting edge biomedicine and biotechnology.

The rationale for such an approach is that quaternary prevention has until now usually been directed at strategies and technologies that have already been implemented or are amenable for objective study. While it may be scientifically satisfying to judge only what one can count and observe in the present, it is (as I have elaborated above) increasingly being recognized that medicine is shaped in the future, that is through the making of guiding visions (Guston & Sarewitz, 2002; Selin, 2008; Borup et al., 2006). The future is increasingly recognized as a contested space, appropriated and colonized by technoscientific biomedicine. Quaternary prevention must take part in this contest, shaping the visions of the future so as to avoid undue waste and harm. Brave new predictions have to be met by critical predictions. As Petersen (2009) states, "the role of expectations in shaping thinking and action needs to be taken seriously by those who are concerned about the ethical implications of biotechnologies".

A prospective, proactive quaternary prevention could draw on theory, methods and experience from several fields, including the medical and the sociology of the future and expectations and real-time technology assessment. This would mean a new frontier in scientific responsibility.

8.6 Some weaknesses and limitations of the thesis

In this section I will briefly acknowledge some weaknesses of this thesis that have not been addressed above.

8.6.1 Non-scientific speculation about the future?

Writing from the perspective of medicine, I find it reasonable to point out that the empirical nature of this thesis is unconventional. It is based on empirical investigation of a material, but that material is theoretical and future-oriented. Since the analysis focuses on a *proposed*

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plosives are used to promote the proactive, prospective P4 vision: Plosives make an *explosive* sound, as in *"powerful"*.

framework for future primary care, it is (like the proposition it studies) by necessity, somewhat speculative. As one sociologist of the future points out, the predictions of those who criticize the makers of future visions are in many ways not any better than their targets' (Hedgecoe, 2004, p. 177). As I have already discussed in the methods chapter, there is however a need to address the theorizing and future-mongering of biomedicine, and although their results are by no means the results of an accurate science, I think the methods of philosophy, history and social science must be applied.

8.6.2 Broad scope and open questions

This thesis addresses a wide range of topics and opens many thematic doors. Each could have been worthy a thesis. Take, as examples, personalization, personhood, mind, body, the mind-body problem, downward causation (paper I), holism, mechanism, overdiagnosis, medicalization, biomedicalization, biohealth, biopolitics (paper II), clinical utility, actionability, risk, prediction (paper III). From a philosophical perspective, one might argue that the topics and concepts are too many and too superficially addressed. I however believe that, from the generalist perspective of primary care, it is pertinent to address systems medicine as a whole to gain the necessary overview. This would be incompatible with a thorough discussion of each element. The vision in question also fleetingly brings up all of these concepts in its promises, and it seems impossible to formulate a critical counterargument if one also does not address each of the elements.

Also, while a wide range of topics *are* addressed and touched upon, the thesis also leaves questions unanswered. I fully realize that I have not explored systems medicine in full, and there is ample room for further research.

It should also be underscored that the concepts of ”systems”, ”systems biology” and ”holism” in systems biology may have many different meanings – perhaps as many as there are systems biologists. My thesis has had to simplify what systems medicine is in order to generate a coherent argument that is not overwhelmingly detailed and long. A main strategy has been to refer to, on the one hand, a theorist who defines an extreme of systems biology, a very particular expression of its thinking (Denis Noble), and, on the other hand, the very mainstream of systems medicine as defined by a PubMed search and a focus on Leroy Hood,

its most prominent visionary. There are many other leading theorists that could have been highlighted more (e.g. Olaf Wolkenhauer, Hans Westerhoff and Hiroaki Kitano).

8.6.3 Ignorance of quantitative models

In producing this thesis, I have focused almost exclusively on the theory of systems medicine as expressed in plain language, as philosophical concepts (e.g. downward causation). However, the core theory of systems biology and medicine is to a large extent defined by the mathematics of its models. As quoted in paper II, Moreno et al., (2011, p. 313), describe the theory of systems biology as…

> ...the set of mathematical and computer simulation models and tools that have been developed to study network architectures and dynamics. Although there is no unified branch or corpus of mathematics that constitutes network theory, there exists however an increasingly indispensable 'tool-kit' of methods and disciplines that merge into what we might call network theory: this ranges from dynamical systems theory to network topology, from random boolean network models to coupled oscillators. The study of networks with strongly and recurrently interacting components allowed scientists to deal with holistic systems, showing that, despite their variety, they share certain generic properties.

At the beginning of this thesis the study of mathematics or information science was far from my scope. I did, however, complete Phd courses in Mathematical biology and Molecular Physiology. If I had the chance to start again, I would have devoted more time to mathematics in order to come closer to the models of systems medicine. Insight into their mathematics would likely have strengthened the argument.

8.7 Future research

This thesis points towards a number of avenues of further research and theorizing as medicine develops.

8.7.1 Conception of persons, patients, health and disease

The thesis points towards more work on the concepts of downward causation, and biological relativity as key, integrative concepts for medicine, especially bio-psycho-social medicine and

as guiding concepts for understanding medically unexplained problems that escape mechanistic reductionism. Other systems biological concepts may also be further investigated, criticized and perhaps usefully integrated into medical theory, e.g. robustness (see Definitions and Key concepts). More research can be done in order to create a conception of the human organism that satisfies both scientific and humanistic needs. For a long time, it has been as if biomedicine and humanistic medicine have been talking about different creatures, but I think there are opportunities in conceptualizing life and humans in terms that may at least narrow the gap. In paper I, I point out that there is much conceptual work going on in systems medicine and relevant philosophy of biology that has great potential for understanding of patients (see its p. 948 and references therein). An especially interesting example is Marc Bickhard´s work on conceptualizing persons (Bickhard, 2013). I also noted (see last paragraph) that, ”The similarities and differences between Cassell and Noble may also serve as one fruitful point of departure for further work in developing a future unifying theory of medicine”. Rather than reifying aspects of the body, both theorists seek to unify what is called ”mind” and what is called ”body” under the heading of ”activities”. Their joint emphasis this ”doing-ness”, or agency, of living processes seems one avenue forward. The following two quotes from paper I of this thesis highlight my point:

Denis Noble:

> ”The significance of this way of expressing things is then best brought out by noting that Descartes’ famous philosophical statement ‘I think, therefore I am’ (cogito ergo sum) could be more minimally expressed as ‘thinking, therefore being.’ ‘Thinking’ requires that a process exists, just as ‘going’ does, but it does not require that we should reify that process”.

Eric Cassell:

> ”The word mind is useful as a label for a whole bunch of activities that are characteristic of persons such as thinking, reasoning, assigning meaning, dreaming, imagining, creating, emotions, and others. You will find, that (. . .) you can easily do without the noun mind. One merely needs to substitute the word for the activity – thoughts, imagining, reasoning, willing, and so on”.

I think that a useful, more unifying medical theory may be generated by picking up on the theoretical elements that explain the similarities of these statements.

8.7.2 Future research on the utility of systems medicine

The thesis also points towards more research on the utility and responsibility of future systems medicine, both in terms of more traditional empirical assessments and vision-focused quaternary prevention (see Discussion above on proactive quaternary prevention). Medicalization, overmedicalization and overdiagnosis should be key concepts here. One particular topic that has not been addressed in-depth, and that may serve as an important example of questions that need to be addressed, is the methodological feasibility of so-called n=1 studies employing a continual stream of big data on the individual who serves as his/her own control. How can we know when we have identified a cause of health problems or improvement in such studies? This methodology needs to be criticized and validated. Herein, I see fundamental questions in the philosophy of causality that are, for example, being addressed in Norway in the CauseHealth project (Anjum, 2015).

A novel concept, the concept of ”scientific wellness” introduced by Leroy Hood, has also gained traction during the course of this project (Arivale, 2015a; 2015b). One clear avenue for ”vision-focused quaternary prevention” is to turn one´s attention to this cutting edge concept.

One important topic that also needs further research is to develop the concepts of actionability and clinical utility. What does it mean for a test or finding to be actionable? This is currently vague in systems medicine.

8.7.3 Ethics of overpromising

In this project, I have also become more aware of the role the creation of expectations and hype play in biomedicine. As previously realized by Efstathiou and Nydal (2014), it is important to work further on when such visions are immoral, if and when overpromising should be sanctioned against, and how.

CONCLUSION AND FINAL REMARKS

9. Conclusion

I conclude that the vision of systems medicine as *a holistic framework for personalized medicine that will bring about a revolution in the the utility of primary care medicine through prevention* is unreliable and should be considered with skepticism. Systems medicine can currently not be considered as truly holistic, personalized or humanistic as in taking into account all relevant components of human biocomplexity. In systems medicine I also find a rising field partly at odds with itself, with conflicting lines of thought as to the nature of life and its own potentials. Today, its dominant technoscientific holism faces fundamental conceptual and methodological problems in countacting fragmentation, in quantifying health, and in prediction and in control of the human organism that it cannot with any confidence be expected to overcome. Besides fundamental problems of unpredictability of complex systems, there are fundamental differences between knowing machines and knowing living human beings, or persons (Strand et al., 2014). A computational model of a person can only come to resemble an advanced selfie, a computational mirror image, of a human. The ultimate humanistic goal, to *know thyself,* can not be reached through technoscientific modeling only; there is a difference between ”knowing thyself” and ”knowing thyselfie”. Therein lies the gap between the science and art of medicine. However, this may not necessarily prevent systems medicine from creating an image of the human body, which computers are most adept at deciphering. The emerging myriad of computer algorithms of mainstream systems medicine that we are witnessing today was accurately described already in 1969 by its own father figure, biologist Ludwig von Bertalanffy:

> “Professions and jobs have appeared in recent years which, unknown a short while ago, go under names such as systems design, systems analysis, systems engineering and others. They are the very nucleus of a new technology and technocracy; their practitioners are the ’new utopians’ of our time (…) who – in contrast to the classic breed whose ideas remained between the covers of books – are at work creating a New World, brave or otherwise (…) [48] The dangers of this new development, alas, are obvious and have often been stated. The new cybernetic world (…) is not concerned with people but with ‘systems’; man becomes replaceable and expendable. To the new utopians of systems

[48] Bertalanffy was a friend of Aldous Huxley, the author of ”Brave New World” (1932). His book General System Theory (1969) is dedicated to Huxley.

> engineering (…) it is the 'human element' which is precisely the unreliable component of their creations. It either has to he eliminated altogether and replaced by the hardware of computers, self-regulating machinery and the like, or it has to be made as reliable as possible, that is, mechanized, conformist, controlled and standardized" (Bertalanffy, 1969, pp. 3 and 7).

In the participatory aspect of P4SM, in which systems medicine is promoted as the harbinger of freedom itself, lies not only a potential for liberation, but for subjecting onself to continuous surveillance in a regimen of control that might ultimately pave the way for oppression. In making the attempt at predicting and controlling human wholes, it is envisioned to launch an unprecedented degree of medicalization that comes with risks of waste and harm. These dangers have not been judiciously considered by its visionaries.

We are living in exciting times. Just as biological super-science mingles with the bright stuff of dreams and P4SM rises, medicine has come to a deeper theoretical appreciation of its own potential downsides (highlighted in the BMJ "Too much medicine" campaign). Systems medicine has not internalized these realizations. It is not a mature vision, and yet it is in the process of changing the future. As another luminary of biology Carl Woese (2004) states: "A society that permits biology to become an engineering discipline, that allows that science to slip into the role of changing the living world without trying to understand it, is a danger to itself". For this reason systems medicine must be further scrutinized through a novel, proactive quaternary prevention that continues to direct a theoretically based focus on its limitations as well as alluring potentials. With the recent US presidential election as a fresh memory, we are today facing a future in which the public, driven by the opportunities of new technologies, of a democratization of information (good and bad), may revolt against what is perceived as detached elites. People may also come to revolt also against a medical establishment that has promised too much, creating expectations that make what has already been achieved seem disposable. We cannot afford such overpromising and the rage that is fuelled by unfulfilled dreams.

10. Final remarks: The Body is already working

I will begin the ending of this thesis where historian of medicine, Roy Porter, trailed off 20 years ago, in a publication that coincided with the peek of expectations to the Human Genome Project and the advent of systems biology:

> ”The close of my history suggests that medicine’s finest hour is the dawn of its dilemmas. For centuries medicine was impotent and thus unproblematic. From the Greeks to the first World War, its tasks were simple: to grapple with lethal diseases and gross disabilities, to ensure live births and manage pain. It performed these with meagre success. Today with ‘mission accomplished’, its triumphs are dissolving in disorientation. Medicine has led to inflated expectations, which the public eagerly swallowed. Yet as those expectations become unlimited, they are unfulfillable: medicine will have to redefine its limits even as it extends it capacities (Porter, 1997, p. 718).

How can systems medicine redefine its limits as it extends it capacities? I would like to suggest, by fundamentally coming to terms with the nature of (human) life. It has the potential.

10.1 Hygeia and Asclepios

In his book ”The Mirage of Health” (1959), biologist René Dubos referred to two ancient gods of medicine to describe two different approaches to health: Hygeia and Asclepios.

Hygeia was not directly involved in medical treatment, rather she was the guardian of health through advocating a balanced life lived in accordance with reason, the ideal of *mens sana in corpore sano*, a healthy mind in a healthy body. She represented the more difficult task of living wisely rather than constantly seeking out and depending on healers. She represented a holistic way towards health, a strategy based on respect for the natural order of things and ensuring an environmental context in which it was possible to live healthily, ranging from plumbing via economy to freedom. Crucially, Hygeia was traditionally associated with tolerance towards the human body, and a belief in its self-healing powers: Given a favourable context, the body should to a considerable degree be expected to take care of itself. As a

philosophy of preventive medicine, this brings to mind the slogan for successful architectural convergence of simplicity and function: Less is more.[49]

Asclepios, The First Physician, by contrast, did not teach wisdom or balance in the same way, but acquired his greater following through the skilled use of technology: Asclepios was self-assured and not tolerant like Hygeia. He proceeded to correct any abnormality with knife and drugs reductively. He was not to be restrained. More is more.

10.2 Asclepios conquering Hygeia

Since the dawn of Western medicine, these two faces of medicine, the Hygeian and the Asclepian, have always coexisted. However, Asclepios, the more spectacular of the two, has tended to dominate, guiding and being driven by new tools and scientific discovery. The Hygeian tradition was not scientific like the Asclepian, ”unless a life of reason be considered a prerequisite to science” (Dubos, 1959, p. 134).

Mainstream systems medicine as currently proposed can be seen as Asclepian medicine taken to an absolute extreme. To rephrase my finding on ”holistic medicalization”, P4SM represents the conquering of Hygeia by Asclepios. It is directed towards the replacement of reason and wisdom by quantification, technological precision, constant monitoring and correction of all components of the complexity of life. It is the calculation of the good life. It is ethics and aestetics replaced by metrics. It risks filling the Hygeian holism and faith in the self-maintenance of the body with Asclepian intolerance. Living itself becomes a constant Asclepian enterprise.

Systems medicine is an approach that, as it stands, promises to achieve ”less” (waste and harm) through much, much ”more” medicine. Its premise is that ”more” will create benefits that outweigh the inevitable downsides of ”even more”. It postulates that the result of tackling all components of complexity through an Asclepian approach will somehow be ”*less*”. However, as previously stated, this vision is unreliable and not necessarily realistic.

[49] ”Less is more” is a phrase attributed to the German-American architect Mies van der Rohe (1886-1969) (Mertins, 2014). It represents the minimalist ideal of modern architecture to reduce buildings and their components into simple forms so that a fuller result could emerge.

However, on the creative side, systems medicine also contains the remedy, the seed of its own balance: a more sophisticated, biomedical understanding of life. The intolerance of medicine is, I think, partly based on the continued view of the body as a machine. Machines rust. They constantly disintegrate. Causation is bottom-up, one way, from the parts to the whole. If the body were a machine, it certainly needs regular maintenance. However, the human body is not a machine in any conventional way. It is alive, it is self-maintaining, self-replacing, to a degree self-sufficient. It possesses, in a word, *downward causation*, which, according to some systems biologists, should be seen as the guiding principle of systems medicine.

10.3 Less is more: Call for a Hygeian systems medicine

A 2005 article by systems biologist Denis Noble, whose book "*The Music of Life*" inspired this whole project, was entitled "*The Heart is already working*" (Noble, 2005). What Noble was referring to, was the fact that his own research on cardiac physiology had already shown the feasibility of the systems approach. So, in this article, he voiced optimism that systems biology may help us understand other aspects of the human body. However, I will here interpret the phrase "The Heart is already working" in a different sense (that I believe Noble would agree to): That his research had shown how the pacemaker-cell and the heart is a self-orchestrating system, an entity, which is in an important sense "already working" without interference: An entity that could not be understood by looking at, or working with, the parts. The oscillator of the pacemaker rhythm exists not at the levels of DNA or protein networks; it is integrated at the level of the cell. This is the Music of Life (2006).

By contrast, mainstream systems medicine with its goal of constant monitoring, its constant tampering with minute abnormalities *ad modum Hood* (Arivale, 2015a; Paper III) is quite literally to treat the body as something that cannot, not at any time-point through life, be trusted and left to its own devices. Between the lines, this kind of systems approach suggests very forcefully that *the body is not working*. Not even the body perceived as healthy is working well enough. It is replete with actionable possibilities. And although the idea that we are disintegrating is in some instances true, especially in old age ("everybody dies", as Eric Cassell bluntly states), it is far from the whole truth. I think this is the core folly of medicine in general and preventive medicine in particular: It assumes that it can be very much more efficient than the already fine-tuned body is in taking care of itself. It may however prove

surprisingly hard to make the healthy healthier, the living more alive. Blinded by the machine metaphor, the ill-informed engineer proceeds to interfere, risking more damage than gain.

As a corollary, systems medicine assumes that it can know humans better than humans by constructing a very advanced machine. It is easy to believe that a machine can understand humans better than humans when the human body is already construed as a machine. What could be more logical? And again, in many instances, machines *are* superior in making sense of data from the human body. The mechanistic prejudice is in many instances confirmed. So here we are, at a historical juncture, with a computer, an artificial intelligence, pitted against a human being (the clinician facing the patient) in a contest of who is best at understanding what the human being needs. All the sophistication of computational algorithms and mathematics engaged in a historical confrontation with billions of years of evolutionary training (plus education and experience) in the task of knowing personal health, a valid human goal and a meaningful action.

As a contrast to this I call for a Hygeian systems medicine. One which is based in the scientific recognition that the body is a robust system, largely self-caring, self-maintaining as long as it has an environment to live in which is reasonably fashioned. A robustness-based, downward causation-based systems medicine. It is usually said about complex systems and emergence that *the whole is more than the sum of their parts*. However, as complexity scientist Fulvio Mazzocchi (2008, p. 12) puts it, ”The whole” is in another critically important sense, ”not only more than the sum of its parts, but also less than the sum of its parts because some properties of the parts can be inhibited by the organization of the whole”. This is, I think, the conceptual essence of a medical ”less is more” strategy. This is the reductionism, the possibility of simplicity, inherent in holism: *The whole is less than the sum of the parts*. In focusing on wholes, one may organize the parts beneficially. And, just as importantly, be tolerant of the body and let it organize itself. Leave space for downward causation. More biomedicine, more parts-focus, is not always better. It is the *combination of holism and intolerance* – Asclepian holism – that paves the way towards holistic medicalization. However, a holism without Hygeia is unreasonable and unsustainable. Only recently, a Nature article highlighted how each of us carries a number of ”lethal” mutations that do not in practice do any harm, likely in part because their effects are buffered by the redundandy or robustness of the system. Findings like this promote a new understanding of medical genetics that is no longer ”bottom up” (Hayden, 2016). Silently, they point towards Hygeia.

As a corollary, a so-called ”middle-out approach” to knowing the organism, based on the appreciation of downward causation and the folly of a one-sided bottom-up approach, has been proposed for systems medicine (Noble, 2005; 2006). Here, one starts with the level one can access (e.g. the patient in front of you) and then proceeds to connect this level to DNA ”below” and the person’s close relationships and environment ”above”. Importantly, it recognizes that there are aspects of human life that cannot be modelled computationally in a valid manner. Noble reminds us that we do not have to study our brain states to know, for example, that we act intentionally. He writes, ”(…) when we start to talk about the location of the self, we are talking about a person. Such talk belongs to a context in which it makes sense to refer to persons” (Noble, 2006, p. 134). As father of systems biology, Ludwig von Bertalanffy also stressed, one needs “verbal models” formulated in ordinary language to serve as “guiding ideas” (i.e. conceptual tools and metaphor):

> “There are (…) many aspects of organization which do not easily lend themselves to quantitative interpretation. (…) So we have to content ourselves with an “explanation in principle,” a qualitative argument which, however, may lead to interesting consequences” (Bertalanffy, 1969, p. 47).

Ultimately, then, although its tools will certainly lead to important and useful insights, systems medicine must recognize that, to faithfully model a human being, it is necessary to be a human being.

This is another important aspect of body´s ”self-sufficiency”; it can already model itself. The body is not blind to its own health and may need limited help in prediction. Epistemologically and methodologically it is interesting to observe that *self-rated health* has been shown to a strong predictor of the hard end-point of mortality (Idler & Benyamini, 1997; Schnittker & Bacak, 2014). I suggest that self-rated health should become a key parameter for personalized systems medicine that should be nurtured by technology. Self-rated health may even be a useful predictor of allostatic load, a key systems biological concept that has also been proposed as central to the systems medicine framework (Sagner et al., 2016; Vie et al., 2014).

In the end, beyond evidence and theory (what is scientifically and philosophically true) and ethics (what is morally right) we find *aesthetetics* (concerned with what is beautiful) as a guide to living. Fundamentally, I think there is something deeply unaesthetical about living your life as if you are constantly falling apart. It amounts to a profound lack of self-esteem. Like a frightened bird constantly surveilling the deadly ground even though it should know it

can fly. There can be no healthy mind in a healthy body in the presence of a constant focus on disease, risk and suboptimality. This represents no ”holistic 360-degree view of you”, as promised by the first systems medicine clinicians (Arivale, 2015b). To achieve such a view, one must raise one´s gaze from the parts and the ground below. Optimistically, I predict that systems biology will continue, as it develops its theory of life, to show that it is unreasonable to constantly monitor, to constantly tamper with all components of its complexity. Come now… *The Body is already working*.

DEFINITIONS AND KEY CONCEPTS

- **Actionable, actionability**. The term "actionable", which is closely related to clinical utility, is frequently used in the systems biological literature, especially in the publications of biologist Leroy Hood. Hood and Flores (2012) state that, "Actionable' means that the data provide information that is useful for improving the health of the individual patient". However, as one white paper on personalized medicine from 2008 states: "As data accumulates ever more rapidly and the demand for standards increases, we will need to focus on the question of what constitutes actionable medical evidence. It will become increasingly important to have defined standards of evidence that will satisfy doctors and patients as they make health decisions, and that will be useful for regulatory and reimbursement purposes" (Leavitt, 2008).

- **Attractor**: A concept used in dynamical systems theory. According to biological anthropologist Terrence Deacon (2012), "An attractor is a 'region' within the range of possible states that a dynamical system is most likely to be found within. The behavior of a dynamical system is commonly modeled as a complex "trajectory of states leading to states" within a phase space (typically depicted as a complex curve in a multidimensional graph). The term is used here to describe one or more of the quasi-stable regions of dynamics that a dynamical system will asymmetrically tend toward. (…) An attractor does not "attract" in the sense of a field of force; rather it is the expression of an asymmetric statistical tendency".

- **Boundary condition**: See *medium downward causation* below.

- **Causation:** The concept of causality or causation is itself subject to vast discussions and may have different meanings in different disciplines. According to philosophers Darden and Tabery (2009), "Causes are often conceived of as being difference makers, in that a variable (i.e., an entity or activity in a mechanism) can be deemed causal when a change in the value of that variable would counterfactually have led to a different outcome". In medicine the concept of causation has often been tied to epidemiological methods. The epidemiologist Sir Austin Bradford Hill (1965) presented criteria for judging if a statistical association implied causality in epidemiological research ("the Bradford Hill criteria"):

- Strength of association
- Consistency of association
- Specificity of association
- Temporality – i.e. exposure must precede outcome
- Biological gradient
- Biological plausibility
- Coherence with other facts
- Possible to confirm by Experimentation
- Analogy (i.e. recognition of resembling patterns)

The criterion of Biological plausibility is also tied to the idea of causation dominating the basic sciences. In the basic sciences of medicine causation has often been tied to mechanisms as in parts in interaction.
Editors of a theme issue on downward causation in Interface, Ellis et al., (2012) give the following definitions of causation:

- "*As production*: a productive cause of an effect is the set of factors that produce, bring about or make happen the effect. It is controversial whether causation in this basic, metaphysical sense ever obtains outside the realm of fundamental physics. (*Causal closure-denying emergentism* maintains that it does so obtain.) And on some philosophical views, there are no productive causes in this sense, only patterns of counterfactual dependence among types of events.
- *As counterfactual dependence*: B counterfactually depends on A just in case B would not have occurred had A not occurred. Patterns of covariant dependence clearly obtain at many levels of nature, not just in physics. Plausibly, it is this minimalist notion of causation that guides methods for drawing causal conclusions from statistical data.
- *Top-down* (see "downward causation").

According to Coffman (2011), we can classify the concerns of scientific inquiry according to the four causal categories established by Aristotle: material (substances), efficient (mechanisms), formal (circumstances), and final (needs)" (this distinction is briefly mentioned in Paper I).

- **Clinical validity and utility**: Clinical validity of a test is "the accuracy with which a test identifies a patient's clinical status" and clinical utility is "the risks and benefits resulting from test use" (Burke, 2014). The latter concept is closely related to actionability. There is currently a debate on how broadly clinical utility should be defined and which factors should be included in the evaluation of clinical utility.

- **Complexity**: Complexity is a concept that is both central to this thesis and at the same time somewhat vague. According to Morin (2007), "the first meaning of the word comes from the Latin complexus, which means what is woven together". No coincidence, the word "context", also from Latin, also originally meant, "to weave together" (con + texere) (see Oxforddictionaries.com). This showing the ancient overlap between the concepts of complexity and context. Reflecting today´s conceptual confusion, Mikulecky (2001) notes that there are dozens of definitions of complexity and proceeds to state ontologically that, "the world is complex", defining complexity negatively as "the property of a real world system that is manifest in the inability of any one formalism being adequate to capture all its properties". According to Bishop (2011), "it is more informative to characterize complex systems phenomenologically. Some of the most important features in these characterizations are:

- Many-body systems. Some systems exhibit complex behavior with as few as three constituents, while others require large numbers of constituents.
- Broken symmetry. Various kinds of symmetries, such as homogeneous arrangements in space, may exist before some parameter reaches a critical value, but not beyond.
- Hierarchy. There are levels or nested structures that may be distinguished, often requiring different descriptions at the different levels (e.g., large-scale motions in fluids vs. small-scale fluctuations).
- Irreversibility. Distinguishable hierarchies usually are indicators of or result from irreversible processes (e.g., diffusion, effusion).
- Relations. System constituents are coupled to each other via some kinds of relations, so are not mere aggregates like sand grain piles.
- Situatedness. The dynamics of the constituents usually depend upon the structures in which they are embedded as well as the environment and history of the system as a whole.

- Integrity. Systems display an organic unity of function, which is absent if one of the constituents or internal structures is absent or if relations among the structures and constituents are broken.
- Integration. Various forms of structural/functional relations, such as feed- back loops couple the components contributing crucially to maintaining system integrity.
- Intricate behavior. System behavior lies somewhere between simple order and total disorder such that it is difficult to describe and does not merely exhibit randomly produced structures.
- Stability. The organization and relational unity of the system is preserved under small perturbations and adaptive under moderate changes in its environment.
- Observer relativity. The complexity of systems depends on how we observe and describe them. Measures of and judgements about complexity are not independent of the observer and her choice of measurement apparatus".

- **Downward (top-down) causation**: The concept of downward causation, first introduced by Campbell (1974), is controversial – just like the concepts of complex systems or life. According to Ellis et al. (2012), "Top-down causation refers to "higher level or systemic features that shape dynamical processes at lower levels". Emmeche et al. (2000) divide concepts of downward causation in three: Strong, medium and weak.
Strong downward causation is the idea that, "a given entity or a process on a given level may causally inflict changes or effects on entities or processes on a lower level" where the upper level is thought to constitute its own substance that is not reducible ontologically to the organization of the constituents. This view amounts to ontological mind-body dualism.
Medium downward causation does not allow the influence of lower levels to have a direct influence on lower levels. "Medium downward causation can be defined as follows: an entity on a higher level comes into being through a realization of one amongst several possible states on the lower level -- with the previous states of the higher level as the factor of selection" (p.22). Boundary conditions is a concept used mainly in mathematics and physics to denote "the set of selection criteria by which one can choose one among several solutions to a set of differential equations describing the dynamics of a system" (p. 24). In natural language, boundary conditions are conceived as "the conditions which select and delimit various types of the system´s several possible developments. The realization of the system implies that one of these typical developments is selected, and the set of initial conditions yielding the type of possibility chosen are thus a type of boundary condition which have been called constraining conditions. They only exist in complex multi-level phenomena on a level higher than the focal level, and are the conditions by which entities on a high level constrain the activity on the lower focal level. On this basis, medium downward causation can be reformulated as follows: higher level entities are constraining conditions for the emergent activity of lower levels (…) the higher level constrains which higher level phenomenon will result from a given lower level state".
Weak downward causation "is conceived as an organizational level, characterized by the organization, the whole, the pattern, the structure, in short the form into which the constituents are arranged (…) one possible way of describing weak downward causation is by using the phase-space terminology invented by qualitative dynamics. Phase space maps all the possible states of the system into a space defined by a set of dimensions, each of them corresponding to a parameter of the system. (…) An attractor is the name of a set of points in the phase space in which many different initial conditions end. (…) it seems to be the case that emergent higher levels are regulated by stable and complicated attractors for the

dynamics of the lower level, often characterized by cyclical mechanisms of regulation. Hence, in the biological case, organisms can be regarded as consisting of highly complicated attractors for the behavior of molecules in a biochemical space".
Both medium and weak downward causation may be interpreted as formal causality (See Causation and Paper I) and conforming to the principle of supervenience (see Supervenience).

- Determinism: Mazzocchi (2008) defines determinism as "the concept that every phenomenon in nature is completely determined by pre-existing causes, occurs because of necessity, and that each particular cause produces a unique effect and vice versa. This, naturally, also sustains the idea of predictability".

- **Emergence, emergentism**: Emergence is, along with the related downward causation concept, the key concept of complex systems. As with the other concepts there are many different, conflicting accounts. According to Mathematician George F.R. Ellis et al. (2012), different ideas of emergence can be categorized as:

- "Predictive: systemic features of complex systems that could not be predicted (practically speaking; or for any finite knower; or for even an ideal knower) from the standpoint of a pre-emergent stage, despite a thorough knowledge of the features of, and laws governing, the systems' parts (Diachronic).
- Explanatorily irreducible: systemic properties and dynamical patterns of complex systems that cannot be derived from laws governing more basic systems (Synchronic).
- Productive causal: systemic properties that exert a non-redundant, productive causal influence on the behaviour of the system's more fundamental parts. Implies that fundamental physics is not 'causally closed' in the sense of there being, for any fundamental physical state, a complete set of determinants that is entirely composed of same-level fundamental physical states" (See top-down or downward causation).

- **Epiphenomenalism**: "The thesis that certain high-level proper- ties (e.g. of mental states) exert no causal influence over other states. These properties would have causes but would not be causes in turn" (Ellis, 2012).

- **Epistemology**: According to systems biologist and philosopher Derek Gatherer (2010), epistemology is "the branch of philosophy dealing with what can be known and how we know it". According to Bishop (2011): "Roughly, ontic states and properties are features of physical systems as they are 'when nobody is looking,' whereas epistemic states and properties refer to features of physical systems as accessed empirically.(…) Predictability of systems has much to do with epistemic states while determinism has to do with ontic states".

- **Exposome**: "The exposome is composed of every exposure to which an individual is subjected from conception to death. Therefore, it requires consideration of both the nature of those exposures and their changes over time" (Wild, 2012).

- **Genotype, phenotype and phenome**: According to systems biologists Gjuvsland et al. (2013): "The terms genotype and phenotype were introduced by the Danish plant physiologist and geneticist Wilhelm Johannsen in 1909. An individual's genotype denotes the constitution of parts or all of its genetic material, while its phenotype may comprise anything from a single observable characteristic or trait to all conceivable ones. Thus any morphological, developmental, biochemical or physiological property all the way down to the subcellular level (including epigenetic marks), as well as any of the individual's behaviour and products of behaviour, is a phenotypic characteristic and belongs to the individual's phenome".

- **Mechanism**: The concept of mechanism is also associated with long philosophical discussions and conflicting accounts of how it should be understood (see e.g. Richardson & Stephan, 2007). I understand it in what I take to be the dominant medical sense, formulated here by philosopher of Medicine, Paul Thagard: ”A mechanism is a system of parts that operate or interact like that of a machine, transmitting forces, motion, and energy to one another. (…) The sciences employ different kinds of mechanisms in their explanations, but each involves a system of parts that change as a result of the interactions among them that transmit force, motion, and energy. Mechanical systems are organized hierarchically, in that mechanisms at lower levels (e.g. molecules) produce changes that take place at higher levels (e.g. cells)” (Thagard, 1999). Here, mechanism is associated with causal reductionism or ”upward causation”. It may be understood as non-organicism, where organicism is the attempt to bridge the gap from a mechanistic understanding towards a full understanding of life (see below).

- **Medicalization**: ”Medicalization can be defined as the process by which some aspects of human life come to be considered as medical problems, whereas before they were not considered pathological” (Maturo, 2012). See also my own definition in paper II.

- **Methodology and method**: Methodology is ”a system of methods used in a particular area of study or activity” where method is ”a particular procedure for accomplishing or approaching something”, e.g. for gaining knowledge about a phenomenon (see oxforddictionaries.com). According to Andersen and Hepburn (2015, p.1), a methodology is ”a particular characterization of scientific method”.

- **Model**: According to philosopher Paul Thompson (2011), ”A ’model’ means a description of the ontology and dynamics of a physical system; this can be achieved using ordinary language but is most often achieved by identifying variables and specifying, mathematically, the relations among the variables and how the variables change over time”. Systems biologists Kohl and Noble (2010) state that, “By definition (model = simplified representation of reality), all models are partial descriptions of the original, whether they are conceptual (to think is to model!), mathematical/computational, or experimental/clinical”. Similarly, philosopher James Marcum provides the following definition: “By model is meant an idealized notion or representation of a system or phenomenon that is proposed as a theoretical explanation or a construct. (…) They represent a phenomenon or system and are used to explain it, often from an abstract perspective. (...) Part of that power is the ability to predict future events. Models then can assist in visualizing how the natural and social worlds operate and in manipulating those worlds for better or worse” (Marcum 2008, p. 8). Complexity scientists Paul Cilliers (2013) also provides a similar broad definition of ”a model”: ”The notion of a model is central to scientific understanding. The notion will be used here in a wide sense; i.e. theories and systems of rules can also be seen as models. To the extent that novels and works of art increase our understanding, it is useful to see them as “models” as well. Models, in short, are what we use to generate understanding”.

- **Omics**: ”The ending ´ome´ means ´totality´” (Noble et al.,2012, Chapter 7). According to systems biologist Michael Benson (2016): ”The term omics is derived from systems-level studies of all genes or gene products. For example, genomics refers to all genetic information for an organism, including genes and noncoding sequences. Other examples include transcriptomics (all coding and noncoding RNAs), metabolomics, lipidomics and proteomics. There are currently many different technologies for omics analyses”.

- **Ontology**: ”The branch of metaphysics dealing with the nature of being” (see oxforddictionaries.com). According to philosopher Robert C. Bishop (2011): ”Roughly, ontic states and properties are features of physical systems as they are ’when nobody is looking,’ whereas epistemic states and properties refer to features of physical systems as accessed empirically”.

- **Organism**: “In its most elementary general expression, an organism is a collection of parts (molecules, cells, and so on) that put together an integrated whole, according to an arrangement that allows it to act in its environment in order to maintain and reproduce itself. Thus, the organization of organisms implies that the component parts and processes of the organized entity are not only responsible for producing each other and the whole, but get actually subjugated under the power of that entity to carry out global, highly coordinated, actions: i.e., to behave like an agent.” (Ruiz-Mirazo et al., 2010)

- **Organicism**: Organicism is a position that reflects a dissatisfaction with mechanism and the machine metaphor of life in conceptualizing organisms. It often emphasizes downward causation: ”Organicism is the point of view that living organisms are complex, hierarchically structured systems, whose parts are all functionally integrated into and coordinated by the system. This view is shared by many scientists who are looking for a more appropriate approach to the phenomena of life. Organicism brings thinking about organisms closer to the actual phenomena of life” (Saetzler et al., 2011).

- **Overdiagnosis**: According to cancer- and overdiagnosis researcher Gilbert Welch (2011), overdiagnosis is ”…detection of abnormalities that are not destined to ever bother us”. According to Moynihan et al. (2012): ”While there is ongoing debate about how to best describe the problem, narrowly defined, overdiagnosis occurs when increasingly sensitive tests identify abnormalities that are indolent, non-progressive, or regressive and that, if left untreated, will not cause symptoms or shorten an individual’s life. Such overdiagnosis leads to overtreatment when these ’pseudo-diseases’ are conventionally managed and treated as if they were real abnormalities; because these findings have a benign prognosis, treatment can only do harm. More broadly defined, overdiagnosis happens when a diagnostic label is applied to people with mild symptoms or at very low risk of future illness, for whom the label and subsequent treatment may do more harm than good”.

- **Phenome**: According to systems biologists Gjuvsland et al. (2013), ”...any morphological, developmental, biochemical or physiological property all the way down to the subcellular level (including epigenetic marks), as well as any of the individual’s behaviour and products of behaviour, is a phenotypic characteristic and belongs to the individual’s phenome”.

- **Physicalism/materialism** is “the thesis according to which all higher level properties are realized by arrangements of lower level properties. On this view, there are no metaphysically irreducible properties of conscious or other mental states.” (Ellis et al., 2012, p. 2).

- Predictability: Complexity scientist Fulvio Mazzocchi (2008, p. 12) defines determinism as ”the concept that every phenomenon in nature is completely determined by pre-existing causes, occurs because of necessity, and that each particular cause produces a unique effect and vice versa. This, naturally, also sustains the idea of predictability. According to complexity scientist Paul Cilliers (2013), who in turn refers to complexity scientist Edgar Morin, the inadequacy of ’classical science’ (i.e. traditional biomedicine) can be described by three ways in which it rejects complexity: 1. The principle of universal determinism,

illustrated by Laplace' s Daemon, capable, thanks to his intelligence and extremely developed senses, of not only knowing all past events, but also of predicting all events in the future. 2. The principle of reduction, that consists in knowing any composite from only the knowledge of its basic constituting elements. 3. The principle of disjunction, that consists in isolating and separating cognitive difficulties from one another, leading to the separation between disciplines, which have become hermetic from each other".

- Prediction The concepts of prediction and predictive power is central to this thesis, but are seldom clearly defined in the literature. Here is my definition: Prediction is an attempt at estimating that something that is unexamined or not yet known will actually be the case based on data about a phenomenon. One may predict whether something is the case in the present (e.g. diagnose a disease), but prediction most refers to forecasting something in the future. When making predictions it helps to have prior knowledge. According to physician-philosopher Eric Cassell (2004), previous data about some phenomenon are gathered and we "distill from them a somewhat abstract version that is our knowledge of them and which we can apply in predicting the future". This "distilling" may be seen as the essence of predictive modelling. Predictive modelling may be used to create statistical risk assessments.

- **Quaternary prevention**: "Action taken to protect individuals (persons/patients) from medical interventions that are likely to cause more harm than good. Goal: Reduce overmedicalization (overdiagnosis and overtreatment) and iatrogenic harm" (Brodersen et al., 2014)

- **Reductionism**: This concept, like complexity, emergentism and downward causation (and indeed "system") has been defined in many ways. See also Section 2.1.2. Mathematician George F.R. Ellis et al., (2012) state (with reference to the definition of emergence above): "Reductionism: the antithesis of emergentism. Hence, it comes in at least three varieties:

- Predictive: systemic features of every kind of complex system could be predicted (at least for an ideal knower, not subject to computational and other limitations) prior to the appearance of such systems, based solely upon comprehensive information about the world's most fundamental constituents and their dynamics.
- Explanatory: systemic properties and dynamical patterns of complex systems exhibited over time interval t1–t2 could be derived, in principle, from information concerning the systems' components and their arrangement over t1–t2, together with the laws governing their evolution.
- Productive causal: systemic properties never exert a non-redundant, productive causal influence on the behaviour of the system's more fundamental parts. Fundamental physics is 'causally closed' in the sense of there being, for any fundamental physical state, a complete set of determinants that is entirely composed of same-level fundamental physical states".

- **Robustness** is "…the ability of a complex biological system to maintain stable function in the face of perturbation" (Kitano, 2007).

- **Supervenience**: "the thesis that every high-level property and phenomena is 'fixed' or strictly determined by the global distribution of low-level properties and relations. 'No high-level difference without a low-level difference" (Ellis et al., 2012).

- **System**: "System" is the central concept of this thesis and systems medicine. It has no definitive definition. In fact, if the meaning of a system, its nature and potentials were known,

the riddle of life construed as a system would be solved. According to the Online Etymological Dictionary[50], the word “system” is derived “From Greek systema ‘organized whole, a whole compounded of parts" from stem of synistanai ‘to place together, organize, form in order’”. A basic definition comes from systems scientist Donella Meadows (2009, p. 188): ”System: A set of elements or parts that is coherently organized and interconnected in a pattern or structure that produces a characteristic set of behaviors, often classified as its ”function” or ”purpose”.

- A system is more than the sum of its parts.
- Many of the interconnections in systems operate through the flow of information.
- The least obvious part of the system, its function and purpose, is often the most crucial determinant of the system´s behavior.
- System structure is the source of system behavior. System behavior reveals itself as a series of events over time”.

- **Systems biology**: Systems biology, as a concept that is tied to emergence, complexity and system definitions, also has no clear definition. Systems biologist Olaf Wolkenhauer (2014) provides the following, helpful definition: “Systems biology is the science that studies how biological function emerges from the interactions between the components of living systems and how these emergent properties enable and constrain the behavior of those components. This definition does not only integrate many different views but also highlights the fact that systems biology is not a separate discipline but part of biology and biomedicine. Systems biology is thus an approach to understanding complex, i.e., non-linear spatio-temporal phenomena, across multiple levels of structural and functional organization. And for most projects I have been involved in, this approach is characterized by a combination of experiments with mathematical, statistical, and computational modeling”.

- **Systems medicine**: According to systems biologists Bousquet et al. (2011, p. 5), “Systems medicine is the application of systems biology to medical research and practice”. A number of definitions have been provided otherwise to illustrate the diversity of ideas that characterize the concept:

- “Systems medicine involves the implementation of systems biology approaches in medical concepts, research and practice, through iterative and reciprocal feedback between data-driven computational and mathematical models as well as model-driven translational and clinical investigations” (Kirschner et al., 2013).
- “Systems medicine is a new approach for the development and selection of treatment strategies for patients with complex diseases. It is often referred to as the application of systems biology methods for decision making in patient care” (Gietzelt et al., 2016). “Systems medicine is an emerging discipline, which is based on combining high-throughput (omics) and computational analysis with functional and clinical studies. The basic research aims are to gain systems-level understanding of the molecular changes underlying common diseases, and of how they vary between subgroups of patients who appear to have the same disease. The clinical aims are to use this information to achieve predictive and individualized medicine” (Benson, 2016).
- “Systems medicine is not simply the application of systems biology in medicine; rather, it is the logical next step and necessary extension of systems biology with more

[50] http://www.etymonline.com/index.php?term=system, accessed 2016-05-18.

emphasis on clinically relevant applications. Building on the success of systems biology, systems medicine is defined as an emerging discipline that integrates comprehensively computational modeling, omics data, clinical data, and environmental factors to model and predict disease expression (the pathophenome)" (Wang et al., 2015).

- "Systems Biomedicine can be considered as an emergent branch of Systems Biology that allows zooming through the multiple scales of life and disease by combining reductionist and holistic approaches. A widely applied research concept is a cycle composed of theoretical analysis, computational modelling, and experimental validation of model hypotheses, which drives the refinement of computational and experimental models. The ultimate goal in Systems Biomedicine is to apply mechanistic insights to clinical application and to improve patients' quality of life" (Antony et al., 2012, p. 604).

- **Validity**: Validity is associated with the concept of truth and can be defined as the degree to which our tests, assessments and models actually measure or predict what they are supposed to measure or predict (i.e. the truth or reality). Validity is defined according to specific standards for uncertainty within a field.

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PAPERS I-III

Paper I

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Getting personal: can systems medicine integrate scientific and humanistic conceptions of the patient?

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Abstract

Rationale, aims and objectives The practicing doctor, and most obviously the primary care clinician who encounters the full complexity of patients, faces several fundamental but intrinsically related theoretical and practical challenges – strongly actualized by so-called medically unexplained symptoms (MUS) and multi-morbidity. Systems medicine, which is the emerging application of systems biology to medicine and a merger of molecular biomedicine, systems theory and mathematical modelling, has recently been proposed as a primary care-centered strategy for medicine that promises to meet these challenges. Significantly, it has been proposed to do so in a way that at first glance may seem compatible with humanistic medicine. More specifically, it is promoted as an integrative, holistic, personalized and patient-centered approach. In this article, we ask whether and to what extent systems medicine can provide a comprehensive conceptual account of and approach to the patient and the root causes of health problems that can be reconciled with the concept of the patient as a person, which is an essential theoretical element in humanistic medicine.
Methods We answer this question through a comparative analysis of the theories of primary care doctor Eric Cassell and systems biologist Denis Noble.
Results and conclusions We argue that, although systems biological concepts, notably Noble's theory of biological relativity and downward causation, are highly relevant for understanding human beings and health problems, they are nevertheless insufficient in fully bridging the gap to humanistic medicine. Systems biologists are currently unable to conceptualize living wholes, and seem unable to account for meaning, value and symbolic interaction, which are central concepts in humanistic medicine, as constraints on human health. Accordingly, systems medicine as currently envisioned cannot be said to be integrative, holistic, personalized or patient-centered in a humanistic medical sense.

Introduction

'*Throughout my career, I have been searching for a medicine to which I can belong. For me, medicine will never be a pure and simple place and I will argue that a much more complex but creative and useful place can be defined by the interplay of opposites* [1]'
-Iona Heath, Divided we fail: The Harveian Oration 2011.

Systems medicine [2–4] – defined as 'the application of systems biology to medical research and practice' – has recently been proposed as a future and primary care-centred strategy for health care worldwide [5].

Throughout this exploration, we aim to contribute to an understanding of the strengths and limitations of this framework for primary care. More specifically, we investigate whether it can meet the challenge of providing clinicians with a comprehensive

theoretical framework that can integrate the division between scientific and humanistic medicine.

While scientific medicine (or 'biomedicine') is rooted in the traditional world view of the natural sciences and focuses on diseases associated with bodily *parts*, humanistic medicine can be defined as 'medical practice that focuses on the whole person and not solely on the patient's disease' ([6]: p. 10). The key theoretical element in humanistic medicine is the concept of *the patient as a person*. We pursue the following research question:

> Can systems medicine provide a comprehensive conceptual account of and approach to the patient and the root causes of health problems, and – furthermore – can such an account be reconciled with the humanistic concept of and approach to the patient as a person?

In this, we also seek to shed light on the key clinical challenges of medically unexplained symptoms (MUS) and multi-morbidity. We have chosen to approach the research question through a comparative analysis of the relevant thinking of two key theorists. We analyse the conceptual account of and approach to the patient and the root causes of health problems found in the philosophy of systems biologist Denis Noble [7] and whether it can be reconciled with that found in the primary care-oriented and humanistic medical philosophy of Eric Cassell [8,9]. A broad and comprehensive survey of the relevant theoretical literature on systems biology and systems medicine has led us to state the following premise for this investigation: Within the development of systems medicine, Noble's philosophy is the most humanistically inclined [7,10], and thus representative of how close systems medicine can come to humanistic medicine theoretically. Although Noble may not represent mainstream systems biology, he is influential [5,11–13]. He is much quoted in the theoretical development of systems medicine and also involved in the conceptual foundations of fledgling 'systems psychiatry' [14], which makes him directly relevant to a field that obviously faces the challenge of reconciling scientific and humanistic conceptions of patients. Importantly, his philosophy also represents the most comprehensive account of the relevant questions we have found within the current systems biological literature. Cassell's philosophy is chosen as a representation of humanistic medicine more broadly and as the most comprehensive and authoritative philosophy of patients as persons currently found in humanistic medicine. As such, Cassell's philosophy reflects what Noble and systems medicine must account for in order to bridge the sciences–humanities divide.

Background

The challenges of primary care

The practising clinician, and most obviously the primary care doctor who is confronted with the full and uncategorized complexity of human function and dysfunction on a daily basis, experiences several related challenges. These also represent the ultimate real-life trials that systems medicine – no less than humanistic medicine – has to stand up to in order to prove relevant as a strategy for primary care.

One fundamental need and challenge lies at the heart of medical practice: the necessity of providing a comprehensive conceptual account of and approach to the patient as an entity and of the root causes of health problems.

A second challenge is that, in providing such a conceptual account and approach, medicine takes on a dual philosophical appearance. The clinician is expected to approach the patient in a way that is not only scientifically valid and evidence based, but also sensitive to the full range of human capacities, including individual experience, needs and values. These two aspects are typically expected to *coexist* or *merge* in the concept of *knowledge-based practice*, but exactly *how* such a merger should come about is far from obvious. On the contrary, the doctor is pulled in two different theoretical and practical directions – towards scientific *and* towards humanistic medicine [6]. This reflects a more general division of Western intellectual life, described by CP Snow in 1959 as 'The two cultures' [15]. In what follows, we will describe the sides of this division (asterisks '*' refer the reader to the definitions in Box 1):

At the heart of *scientific medicine*, the branch of medicine that currently dominates the profession's view of what counts as a medical explanation lies the machine metaphor, which depicts all living entities as machines. In this, scientific medicine is materialist*, reductionist and mechanistic [6,16,17]. The patient is seen as 'nothing but' *parts in interaction* and should, as a corollary, be understood, studied and treated by focusing on those parts [6,18,19]. Associated with this conceptualization is molecular determinism or 'smallism' [20], the belief that entities at the molecular scale or level* are *causally privileged*. Accordingly, patients and their functions and dysfunctions (diseases) are depicted as being caused by interacting parts through 'upward' causation [21]. The lower scales or levels*, especially the genome, hold the necessary information to 'inform' the larger scales or higher levels as through a programme [17]. As a corollary, the emergent phenomena that arise from such interactions of parts are given an inferior ontological* status. They are said to be *epiphenomenal* – that is causally insignificant and not as concrete as parts. The patient is considered as a passive and static *thing* rather than an active and dynamic *process* [22]. As mathematical biologist Stuart Kauffman [23] has pointed out, there are no 'doings' in this world view and, accordingly, patients have no real *agency*. Additionally, a dismissal of teleology and final causes* as non-scientific further downplays any goal-directedness, purpose or will in human action [17,24–26]. Smallism also downplays the patient's environmental, especially social and symbolic relations (including the doctor–patient relationship). Even the personal experiences conveyed by patients, notably in the form of narratives, are being denigrated as private or too complex and uncountable for 'objective' scientific study [6,27]. In sum, scientific medicine attempts to reduce the personal or 'psychosocial' to molecular and cellular mechanisms or programs in the brain. However, as this does not make subjective personal experience go away, ontological mind–body dualism* prevails in practice [28].

As indicated by biological anthropologist Terrence Deacon [25], scientific denial of human agency, goal-directedness, purpose, consciousness, meaning and value renders biological understanding of patients *an unfinished business* and encourages the sciences–humanities divide. Relatedly, this depiction of patients encourages technological intervention directed at body parts rather than personal and social factors [29].

Box 1 Definitions

Epistemology is the study of knowledge, of what can be known and how we know it [49].

Ontology is the part of metaphysics concerned with what exists in the universe and how it is structured [19]. **Materialism/physicalism** is 'The thesis according to which all higher level properties are realized by arrangements of lower level properties. On this view, there are no metaphysically irreducible properties of conscious or other mental states' [63]. **Ontological dualism** is the idea that the universe (including persons) is made of two distinct substances, that is, 'mind' and 'matter' [27].

Complexity: There is no consensus on how to define this key concept, but it can be characterized as a property of systems in which entities at a lower level/smaller scale interact non-linearly and dynamically (through time). These interactions result in emergent (novel) properties in the system (whole) that cannot be found in the parts in isolation. The system is then said to display higher degrees of complexity or **organization**. The emergent whole may or may not be taken to have causal efficacy in itself [19].

Levels and scales: According to Noble, **scale** is the size of a system. Systems of different scale may be nested within each other. Examples of **levels** are molecules, cells, organs and organisms. This hierarchy of levels is metaphorical as these entities are not literally on top or below each other. Levels and scales will in the context of patients be correlated [69]. Molecules are (in reality) nested within cells, within organs, within organisms, within an environment at successively larger scales [64]. These scales and levels also correspond to successively higher levels of complexity or organization [70]. A (multicellular) organism/patient is more complex and highly organized than cells or molecules. Noble conceptually prefers the term scale, but nonetheless uses 'levels' metaphorically in causal explanations.

Intentionality: In a phenomenological sense 'consciousness is intentional, in the sense that it "aims towards" or "intends" something beyond itself'. Intentionality may also refer to the purpose or goal-directedness of acts, which is 'only one kind of intentionality in the phenomenological sense' [81].

Types of causes: Aristotle established four causes: 'Material (substances), efficient (mechanisms), formal (circumstances) and final (needs)'. Material and efficient causes answer questions like 'what is this and how does it work?' while formal and final causes answer questions like 'why did this happen?' [24].

Humanistic medicine represents a reaction to this perceived dehumanizing and medicalizing trend. We follow Marcum [6] in broadly categorizing a variety of frameworks and lines of thought as humanistic, including biopsychosocial, patient- or relationship-centred, narrative-based, person-focused and person-centred medicine as well as medical phenomenology [30–37]. Humanistic medicine strives to maintain sensitivity to the full range of human capacities, experiences and needs in medicine, and to integrate what is called 'psychosocial' with biomedicine in the concept of *the patient as a person* [35]. It is currently far from clear, however, just how such an integration can be achieved.

Medically unexplained symptoms and multi-morbidity

The prevailing panorama of health problems represents a *third major challenge* of primary care. Scientific medicine has led to obvious benefits, but a variety of common, complex and costly conditions strongly actualize the challenge of theoretical development. Two key examples are so-called functional disorders or MUS and multi-morbidity. Importantly, systems biological methods are currently starting to be applied to these problems [5,38].

The MUS category encompasses hundreds of diagnostic labels, for example, the chronic fatigue syndrome [39], which represent some of the most common problems in Western medicine [40,41]. The root causes of MUS are poorly understood. However, it is important to note that, when these problems are categorized as *medically unexplained*, they are unexplained in a certain way, namely according to the current ontology and epistemology of scientific medicine. And as they are in fact defined by their very *scientific unexplainedness*, they seem likely to highlight the shortcomings in parts-oriented conceptualizations and explanations of patients and health problems, especially concerning the relations between 'bio', 'psycho' and 'socio' in biopsychosocial thinking [33,39–41].

Multi-morbidity refers to the phenomenon that patients, according to current scientific standards, often satisfy the criteria for many diagnoses. These patients are therefore, by biomedical convention, thought to have many separate diseases, each presumably caused by specific pathogenetic mechanisms related to specific body parts or subsystems, and each correspondingly treated in parts-focused and separate 'silos' of medicine [42]. There is however, emerging evidence, which indicates that many common chronic conditions, which typically cluster and often include MUS, might be produced by pathogenetic life circumstances, sometimes referred to as 'the causes of the causes' [42–44].

The above challenges all trigger fundamental questions relating to *philosophy of science, causality, biology and mind* that involve known dichotomies such as reductionism (parts) vs. holism (wholes), psyche vs. soma, subjectivity vs. objectivity, illness vs. disease and mechanistic explanation vs. meaning [45]. As a consequence, the doctor who professionally seeks to straddle the scientific–humanistic divide, struggles to find a valid reference point [1].

Systems medicine to the challenge

Enter systems medicine. At a first glance, this proposed paradigm intriguingly seems to offer the clinician promises and hope that his/her challenges may soon be catered for by scientific progress. Systems medicine is at once proposed as aiming to tackle *all components of disease complexity** and as being *holistic, integrative*, *personalized* and compatible with *patient-centred medicine* [5]. Systems medicine has also been said to favor a '*novel humanism directed to the management of the patient as individual subject*' [46]. However, the given impression that systems medicine can integrate theoretical elements from 'scientific' and 'humanistic' medicine is not obviously valid and deserves scrutiny.

Broadly conceived, systems biology is a convergence of molecular biology and systems theory [47–53]. Molecular biology

has culminated in 'omics', that is the sequencing of whole bodily 'parts lists', including DNA (genomics), RNA (transcriptomics) and protein (proteomics). The resulting massive amounts of information on parts have not in themselves yielded the sought-after understanding of wholes, predictive power or medical breakthroughs [54]. Rather, it would seem that biology has 'hit the wall of bio-complexity, reductionism's nemesis' [18]. Fundamentally, the connection between parts, especially the genome (genotype), and the whole organism (the phenotype) stands unaccounted for [19,55,56]. The manifest goal of systems biology is precisely to make this connection. Its method is to integrate data on parts, in the context of medicine *'billions of data points'* [5] into explanatory and predictive mathematical (computational) models of patients as wholes (aka 'systems'). Its ambition is no less than to *calculate life* [52].

Importantly, systems biology is not a homogeneous scientific discipline. Although it is clear that systems biology is currently dominated by a highly parts-oriented approach that conceptualizes and investigates patients as networks of molecules [47,48, 51,53,57,58], a minority, exemplified by Noble, seeks a more fundamental philosophical reorientation. Noble also explicitly espouses a humanizing ambition, stating that the focus on lower-level causes in biomedicine may lead to a dehumanizing approach that 'encourages treatment of the disease while ignoring the particular patient who has the disease' [10].

Cassell's humanistic medicine: patients as persons

Such dehumanization is precisely what Eric Cassell and other thinkers who espouse humanistic medicine seek to remedy. Their ambition is to ground medical practice in a comprehensive theory of the patient *as a person*.

Mind and body

As a point of departure in developing such a theory, Cassell describes how the trauma of 9/11 manifested as health problems in affected New Yorkers [8]. He then asks *how and why** such a perturbation – which would often be described as 'emotional' or 'psychosocial' – could have profound impacts described as 'physical'? In approaching such a conundrum (the mind–body problem), Cassell stresses that our current conceptions of 'mind' and 'body' are inadequate. Asking how the mind *affects* the body, and vice versa are the wrong questions because any fundamental mind–body or person–body duality is false and entities that are not separate cannot affect *each other* in a conventional, mechanistic sense.

Instead, Cassell holds not only that the body and the physical participates in everything a person does, but that what we call physical or biological should be viewed as mental, purposeful and social [8]. Persons are *embodied*, they *have* a body, but if the body were properly understood, it would also incorporate all the capacities attributed to 'the mind'.

Agency

In further explaining the unity of mind and body, Cassell depicts the person more as an unfolding process with a history and a future, 'existing through time in a narrative sense' ([9]: p. 28), rather than as a static object. The concept of agency, the ability to act becomes crucial. Cassell emphasizes an *activating* language when conceptualizing persons: 'Persons do things; they act, think, have emotions, create music, express love, get sick, urinate, see and feel things, and more' ([8]: p. 235). What is called 'mind' and what is called 'body' is blurred and sought unified under the common heading of *activities*: 'The word *mind* is useful as a label for a whole bunch of activities that are characteristic of persons such as thinking, reasoning, assigning meaning, dreaming, imagining, creating, emotions, and others. You will find, that (. . .) you can easily do without the noun *mind*. One merely needs to substitute the word for the activity – thoughts, imagining, reasoning, willing, and so on' ([8]: p. 242).

Consciousness, meaning and value

According to Cassell, even conscious experience and perception are bodily activities, and *meaning*, the active labelling of experience so that it has aboutness and significance, is his core concept. Meanings also have important value-aspects and are always subjective [9].

Meaning is to Cassell what unifies what is usually termed mind and body [8]. Meanings do not *affect* the body as a separate thing, meanings *involve* the body and 'include physical manifestations as an essential and irreducible part of the meaning of things' ([8]: p. 263). Importantly, the activities of the person on every level are based on meanings. The person becomes a meaning-creating, meaning-based process or activity.

Purpose, goal-directedness and will

This also means that the activities of the person are purposeful and goal-directed according to some meaning. In other words, they are intentional* and have a teleological aspect. Some actions are automatic, instinctual or habitual, but some are also volitional or *willed* [59].

Particularity, relationality and narrative

To Cassell, the person is a particular case, an individual different from any other person [8]. At the same time, persons are strongly related to their environments, especially to social processes and activities [8].

Crucially, from an epistemological and methodological standpoint, Cassell's philosophy – like humanistic medicine in general – is characterized by the belief that persons and their complexity can be known not only by studying constituents, but from the information and meaning conveyed and generated through human symbolic interaction, notably *narratives*, and that the doctor–patient relationship is an arena for such knowing [8,9].

Parts and wholes

In explaining the unity of the person, mind and body, Cassell also makes important statements about *parts and wholes*. Concerning persons, 'anything that happens to one part affects the whole; what affects the whole affects every part. All the parts are interdependent and not one functions completely separate from the rest' ([8]:

p. 221). The brain is part of the body, important, but in no way identical to, or exclusive, when it comes to defining the mind or person [8].

However, what Cassell seems to lack is a valid *causal* theory of how the whole person (characterized by the properties often designated as 'mind' or 'psychosocial') can affect the parts like genomes, transcriptomes and proteomes (which in reductionist terms represent 'the body'). This shortcoming also reflects a broader theoretical vacuum in humanistic and biopsychosocial medicine [32,41,60].

Noble's systems biology: persons as integrative processes

In his book 'The Music of Life' [7], systems biologist Denis Noble describes an instant where something makes him cry. He then asks a question, which like Cassell's question regarding the consequences of 9/11, invites an answer of *'how'* and *'why'*. He asks: '*So, what caused me to cry'?* This question also fully reflects the complexity of a primary care patient walking into the clinic. It could be anything.

Parts and wholes

Any systems biologist would agree that such a question could only be answered by considering the patient as a *whole*, that is as a complex system or network [53]. A paraphrased[1] *Nature* editorial reads

> "*What is the difference between a live patient and a dead one? One scientific answer is 'systems biology'. A dead patient is a collection of component parts. A live patient is the emergent behavior of the system incorporating those parts [61].*"

Systems biologists will also acknowledge biological complexity, emphasize the inter-relations of entities at all levels and thus also view the patient as open to the environment. Quote Hofmeyr [62]: 'Nothing in an organism makes sense except in the light of context (. . .) Context captures the essence of the systems approach'.

But any agreement among systems biologists in conceptualizing the patient would stop there. For just how systems or wholes and their emergent properties are to be defined ontologically, is a main point of contention [47,48,52]. We may draw a main dividing line between those who emphasize that wholes have some form of causal efficacy over their parts (downward or top-down causation), and those who do not. According to Noble, downward causation is not only what gives living systems their integrity and robustness to stressors and 'distinguishes a functioning organism from a bunch of molecules' [48], it should also be regarded as the main principle of systems biology and a possible 'integrating theme within and across the sciences' [63].

Noble's philosophy is 'anti-smallist'. His theory of biological relativity challenges the reductionist assumption that what is small is causally most important. It is defined by 'the relativistic principle that there is no privileged scale of causality in biology' [64]. This means that what happens at the molecular scale, including the genome, should not be regarded as causally more important than events at the scale of the whole organism, which can also cause events at smaller scales [64,65].

How can this be? Firstly, Noble argues that there is no *a priori* reason to consider molecular scale processes as more important than organism-scale processes. If small were privileged, we should look at even smaller scales than the molecular [64]. Secondly, he supports his theory mathematically: the parts of a system may be represented by a series of differential equations. If only the parts mattered, one would think that the properties of the whole would emerge from these equations. But to model a whole, one needs to reflect the whole and *integrate* the differential equations [66]. Thirdly, Noble refers to physicist Laurent Nottale's theory of scale relativity. This is beyond the scope of this article, but entails a more general principle of relativity of all scales in nature (for details, see [64,65,67,68]). Fourthly, Noble supports his theory with empirical evidence, primarily his own work on the pacemaker rhythm of the heart. Here, the electrical cell potential of the whole heart cell, the rhythm itself, causes the behaviour of the parts 'top-down' [7,22,63,69–71].

How can downward causation be further described? Noble defines it as 'the influence of boundary conditions determined by a higher scale' [64]. Boundary conditions are in turn defined as 'all the structural and environmental conditions that constrain the behaviour of the components' [64]. These *constraints* can also be seen as *feedback* loops. To Noble, the transmission of information goes both ways: from parts to wholes, but also from wholes to parts [11].

Mind and body

According to Noble, the capacities associated with 'the mind' are grounded in matter. However, within these boundaries of materialism* and in line with his theory of biological relativity, Noble does not depict the self, the person or 'mind', as mere epiphenomena [72]. Instead, he asks *'For humans at least, to live is to experience. How can we understand this?'* ([7]: p. 1).

Agency

Time is central in Noble's conceptualization of entities at all scales and levels*, including patients: 'The really significant philosophical difference between systems biology and reductionist biology is that systems biology focuses on processes rather than components' [10]. Whole organisms like patients with their capacities are as important causal agents as lower level processes. The actions of a person in an environment, may just as well serve as a causal explanation as a molecular mechanism. The genome is not 'The book of life' or a programme for the organism. On their own, DNA molecules can do very little. According to Noble, they should more properly be regarded as passive stores of crucial information, a tool that the active, living organism uses [7]. Noble's central argument is that 'the book of life is life itself'([7]: p. 10).

Consciousness, meaning and value

In a similar way, the brain does very little on its own in Noble's view. It is necessary, but not sufficient in explaining consciousness and the other attributes we call 'the mind' [72]. The brain, and its

[1] We have substituted the word 'cat' in the original text with 'patient' to more properly reflect what one is dealing with in medicine.

molecular and cellular mechanisms, is not something that is synonymous with or dictates the self or the person. Even if scientists had been able to reduce the capacities we attribute to 'the mind' to molecules, cells or brains, this is not the level where such phenomena can be seen to exist or be causally explained. Instead, Noble conceptualizes the mind or self, including consciousness, as an integrative, higher level process rather than a thing [72,73]. When Noble uses the word 'meaning', it is in the sense of such higher level processes or wholes giving meaning to DNA by constraining its function: 'The organism itself contains the key to interpreting its DNA, and so to give it meaning' [74].

Purpose, goal-directedness and will

This means that Noble does not use the word meaning in the way Cassell does. However, he does consider intentional action and will to be real [7,71,72]. He accepts teleological explanations at the organismal level, although he underscores that lower level mechanistic explanations may also be sought for the same phenomena [7,71,75]. Although Noble himself does not elaborate on this, biological theorist Stanley Salthe states that 'constraints from the higher level not only help to select the lower level-trajectory but also pull it into its future at the same time' [76]. Noble also mentions one other key concept for systems biology that may play a role in conceptualizing purposes and goals. The constraint of the whole system entails a statistical tendency for it to be drawn towards a certain future behaviour called an *attractor* [64,72,74].

Relationality, particularity and narrative

In sum, what is a person to Noble? It is the activity of a human organism: 'The activity of the brain and of the rest of the body simply *is* the activity of the person, the self' [69]. Crucially, this self or the person is not a simple or passive thing, but a conscious, integrative process with the causal power to constrain processes at lower levels and scales [7,14,73]. In explaining the overall functioning of persons, their activities must be considered in a social and semantic context [7,72,73]. Noble underscores that '(. . .) when we start to talk about the location of the self, we are talking about a person. Such talk belongs to a context in which it makes sense to refer to persons' ([7]: p. 134). Finally, while searching for general principles that govern human biology, Noble quotes Sulston & Ferry on the particularity of the patient: 'The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms' [74].

Analysis and discussion

Could systems medicine, *ad modum Noble*, provide a comprehensive conceptual account of and approach to patients and the root causes of health problems that would enable the building of a bridge towards humanistic medicine *ad modum Cassell*? Would such an account be relevant to primary health care in general and clinical challenges like MUS and multi-morbiditity?

Similarities and integration

Conceptually, the *similarities* between Noble and Cassell are obvious and striking. We would expect Cassell to see the patient as deduced from Noble's philosophy as a more properly understood body or organism than the current depiction found in scientific medicine.

In what we perceive as a mirror image of Cassell's philosophy, time enters the picture in Noble's theorizing and they both seem to lean towards process ontology as opposed to a particle- or thing-oriented ontology and the notion that an integrative theory of human function and dysfunction should have an historical perspective [22,77]. To both, music serves as a metaphor for this process nature of living persons [7,8]. Crucially, Noble, just as Cassell, advocates an *activating* conceptual language based on verbs that convey 'the doing-ness' of living processes rather than nouns [7]. To both, this doing-ness serves to conceptually unify what we call 'mind' and 'body'. As Noble states: 'The significance of this way of expressing things is then best brought out by noting that Descartes' famous philosophical statement 'I think, therefore I am' (*cogito ergo sum*) could be more minimally expressed as 'thinking, therefore being.' 'Thinking' requires that a process exists, just as 'going' does, but it does not require that we should reify that process' [72].

Importantly, Noble seems able to provide a promising theoretical 'bridgehead' towards what Cassell and humanistic medicine are missing: a valid causal theory of how 'bio', 'psycho' and 'socio' actually relate. In Noble's philosophy, the patient at an organismal scale – the self or the person – acts on smaller scale processes by *constraining*, limiting or focusing their interactions and so to determine their functions [64,65,70]. The dynamic organization of the whole *organizes* – or orchestrates – the smaller scale processes. As Noble indicates, downward causation can be depicted as focusing the lower level processes and thus enabling or bringing forth the emergent properties that arise from them and thus serve as a metaphor for agency and intentional action [17,26,70,73]. If information is defined 'as any kind of event that affects the state of a dynamic system' [56], patients continually create novel information through emergence. This information becomes part of the boundary conditions or dynamic organization of the whole and in turn acts as a feedback that makes a difference to functions at smaller scales [12,70]. This makes it possible to consider patients as being their own organizing principles, boundary conditions, feedbacks, constraints and attractors. Noble, like Cassell, also accepts the concept of intentionality and teleological explanations at the level of whole patients. For what kind of cause* is downward causation in terms of constraints? It is not a material or mechanistic (efficient) cause as in parts 'bumping' into each other, which is the standard way of looking at causation in biological science, but more like a formal and perhaps final cause [17,24,25]. As suggested by biologist Jim Shapiro, words like 'downward control' or 'downward regulation' may be more appropriate than 'causation', which connotes mechanisms [11].

Crucially, Noble is also in line with Cassell, when he states that the functioning of the self or person must be understood in a social context.

Relevance to clinical challenges

How may this be relevant to clinical problems like *MUS and multi-morbidity*? Epistemologically and methodologically, the theory of biological relativity implies that, when primary care doctors seek causal explanations for their patients' health problem,

they should not automatically regard smaller scale processes as the most valid focus of investigation. The scale of the living person, constrained by an environment, might be just as valid in understanding how a given trait is integrated or disintegrated. It may well be that medically unexplained symptoms, for example, those constituting the chronic fatigue syndrome [39], simply do not exist, or cannot be explained, at the level of molecules or cells, and that they reflect clinical scenarios where downward causation is especially important to consider. Biological relativity implies that the relevant physiology may be integrated at the scale of the patient in an environment. As a corollary, it may well be that the *disintegration* experienced and observed in such syndromes must be grasped by considering processes at these scales. At what level such integration or disintegration is to be pinned down is, according to Noble, an empirical question [64]. Meanwhile, we hypothesize that medically unexplained syndromes may be 'functional' in a very simple sense: their causal explanation may be found at the level of the context-dependent functioning of patients as persons, and their automatic, instinctual, habitual or volitional activities, including perception itself. It may well be that the very unexplainedness of these syndromes is related to the way traditional scientific medicine tends to leave larger scales out of the causal picture. They may be 'person-level disorders' left unexplained because persons themselves and their interpersonal relations are not considered to be root causes. Similarly, the effects of the doctor–patient relationship, so-called placebo and nocebo effects [78], as well as context-dependent personal experiences like loneliness [79] and other social conditions may also broadly be seen as integrating or disintegrating constraints. Note that, as Noble has pointed out [65], the traditional use of words like 'root' and 'underlying' to describe the most important causes falsely imply that they should necessarily be found at the bottom of some hierarchy of scales or levels. Metaphorically, constraints (downward causation) may perhaps suitably be described as 'overarching' causes in order to communicate their importance as 'the causes of the causes'.

The theory of biological relativity should also lead to a reconsideration of the concept of multi-morbidity and medical taxonomy. The ontological implications of the concept of downward causation would imply that what is considered separate diseases with separate causes may fruitfully be regarded as different manifestations of 'overarching' constraints. What is considered multimorbidities (e.g. different MUS in one person) may causally cluster at the level of patients as persons or their environment. The theory may also lead to a reconsideration of current efforts in disease categorization and the default premise that health problems are best categorized at the level of parts. One example is mainstream systems medicine itself, which seems to focus mainly on how diseases 'cluster at the genetic, molecular or mechanistic level' [5]. Another example is the genome- and brain-focused Research Domain Criteria developed by the National institutes of Mental Health for psychiatry [80].

Differences and remaining gaps

Although Noble's philosophy may contribute significantly to a bridging between scientific and humanistic medicine, there are certain differences with Cassell's and limitations that need to be considered. The most striking difference between the two is the relative absence of the concepts of meaning and value in Noble's writings. Noble also has trouble in fully accounting for consciousness and intentionality. But so has Cassell and science in general [81]. We believe this illustrates a more fundamental shortcoming, what Deacon calls the *unfinished business of science* [25]. In accordance with this, Noble underscores that there is *no genuine theory of biology*, and that systems biology must learn from other fields in developing its 'musicality' of life [10,69]. This points to a fundamental problem for scientists in general and systems biologists in particular: they do not fully know how to ontologically conceptualize their subject matter: living wholes [23,47,49,69,76,81]. The concepts that influence systems biological thought are currently taken mostly from the engineering sciences and physics, and systems biologists often emphasise the commonalities rather than the differences between man and machine [82,83]. If persons are to be considered their own self-organizers and constraints, it is important to note that these concepts do not as yet explain the difference between living agents and non-living entities [84]. For example, it is difficult to know what kind of agency or will is granted to humans when looking at them as their own *self-constraints*. Concerning the concept of attractors as a metaphor for goal-directedness, one must also note that attractors are rule-governed in a way that human beings may not be [85].

So, why did Denis Noble cry? In his book, he explains that the cause was related to his listening to a musical work: 'We would say that the causes of me crying include: Schubert, because he wrote the music; the piano trio, because they played it with such heart-tugging inspiration; and the beautiful context in which I first heard the music and first cried as a result of it. This, we would say, is in my memory and forms the emotional context' ([7]: p. 2). One could add that the crying could also be seen as an act, as caused by someone actively engaging with the music, and as meaningful symbolic communication unique to humans [86]. Human beings are not like conventional pieces of music. As Noble points out, living humans 'play themselves' [7]. And it is exactly here systems medicine faces its deepest challenge. Systems medicine risks reducing patients to systems, while current concepts of systems may be inadequate in comprehensively mapping human functioning [47,85]. Given such caveats, it is interesting to note that conceptual work is ongoing to further such understanding – with great potential for understanding of patients [17,20,22–26,41,56,57,63,76,77,81,87–92].

In addition to conceptual limitations, it is also important to note that Noble and Cassell differ methodologically. For while systems medicine is all about *calculating human life* in mathematical models, Cassell underscores the patient's narrative and the doctor–patient communication itself as key sources of information about living human systems. To Cassell, dismissing personal experience and meaning as unscientific is the cardinal mistake of medicine, it is like 'deploring the fact that patients are human' ([9]: p. xxiv). The humanistic medical interest in narratives stems from the need to grasp the complexity of human biology comprehensively [36]. However, although Noble may well agree, the concept of narrative plays little or no explicit role in his account. This leads to the question: Can systems medicine, defined as a purely quantitative science, tackle the fullness of human biocomplexity, which inevitably also defines the full complexity of human health and disease?

As we have noted, most of systems medicine has a strongly molecularized concept of and approach to patients. It is no coincidence that the website of the influential Institute of Systems Biology is called 'Molecular Me' [58]. However, systems medicine has also been characterized – and must be taken seriously – as *the medical science that aims to study the way wholes constrain their components* [93]. From an epistemological and methodological standpoint, this must mean that, in order to get a comprehensive understanding of *human health*, one must ultimately also consider specifically *human constraints*. In this regard, it is vital to remember that the evolutionarily derived and *key defining features of human biology* are in fact our cultural capacities of symbolic interaction and creation of narratives [94,95]. The theory of biological relativity implies that these human activities should, *a priori*, be considered as important when considering human health as lower-level functions.

This poses a fundamental challenge to systems medical projects: if systems medicine aims to bridge the genotype–phenotype gap, it needs mathematically usable representations not only of parts (genomes, transcriptomes, proteomes, etc.), but also of wholes, so-called *phenomes*. A phenome is a 'characterization of the full set of phenotypes of an individual' [96]. Intriguingly, human 'phenomics' and a Human Phenome Programme have been called for [55]. Taking the integrative perspective of general practice, we support the development of an organismic, wholes-oriented systems medicine [57]. However, no matter how detailed human phenomes may become, it is still difficult to see how systems biologists can mathematically represent human agency, intentionality and values which are linked to the defining human features of symbolic interaction and narrative. Considering that it is unclear how systems biologists are to quantify a human brain or a living human organism with symbolic behaviour and other social relations, an account of *all components of disease complexity*, as promised by Bousquet *et al*. [5], seems outside the scope of quantitative systems medicine. For example, if human agency, including symbolic activities, are causally influential constraints in medically unexplained syndromes, it is difficult to see how systems medicine can faithfully model these very common and costly health problems mathematically as is currently being proposed [38].

This is also important in considering systems medicine as 'personalized'. Systems biologists Wolkenhauer, Mesarovic and Wellstead state that 'personalized medicine (. . .) requires us to know the parameters that define the individuality of the particular patient' [97]. However, given that the constraints of human symbolic interaction and personal narrative are important in defining human particulars, and that these biological features cannot be meaningfully parameterized or otherwise mathematically described, systems medicine as a fully personalizing science also seems beyond reach even in theory. In practice, systems medicine also has the need to develop 'parameters that define the average, idealized, healthy individual' [3].

Significantly, founding father of systems biology, Ludwig von Bertalanffy [98], who originally also inspired George Engel's biopsychosocial model [30], was aware of such caveats. He regarded symbolism as a defining feature of humankind, noted that there are aspects of human biology one cannot expect to formulate mathematically and advocated complementary models formulated in ordinary language. In a way that seems fundamentally relevant today as systems biology is finally set to define medicine, Bertalanffy also cautioned against the dehumanizing potentials of a science that disregards such humanistic concerns:

> *'(. . .) to the new utopians of systems engineering (. . .) it is the "human element" which is precisely the unreliable component of their creations. It either has to be eliminated altogether and replaced by the hardware of computers, self-regulating machinery and the like, or it has to be made as reliable as possible, that is mechanized, conformist, controlled and standardized'* ([98]: p. 10).

Conclusion

We conclude that systems medicine *ad modum Noble* can contribute significantly in reinstating the person in human biology and medicine. But while Noble's theoretical effort within the field of systems biology is a significant step towards bridging the sciences–humanities gap, systems medicine seems likely to remain *incomplete* as a foundation for clinical understanding and practice. Considering also that most of today's systems medicine seems more molecularly focused than Noble, the image of systems medicine as 'holistic', 'personalized', 'patient-centred' or 'humanistic' in the sense being directed towards the 'patient as individual subject' lacks an adequate theoretical foundation at this time. As Noble also makes crystal clear: 'On the one hand, it seems sensible to deal only with what we can observe, measure and understand. This is the pragmatic approach of science. (. . .) On the other hand, it is laughably presumptous to suppose that this resolves all questions about life. Clearly, it can't' ([75]: p. 120).

Systems medicine must therefore be complemented with other methods. Again, Noble seems to recognize this: 'The point is that in practice we *know* when we act intentionally. We don't need to study our brain states to know that' ([7]: p. 125). Narrative-based medicine and phenomenology are examples of candidates for such complementary fields of knowing, and efforts are ongoing in linking human biology to phenomenology [17,36,37,39,40,81].

Hunter and co-workers have stated that systems biological models should be integrated with 'wisdom produced in the research laboratories and in clinical practice' [4]. We suggest that the wisdom of experienced general practitioners [1] and core challenges like multi-morbidity and medically unexplained symptoms should serve as reference points of primary care complexity in the development of systems medicine. The similarities and differences between Cassell and Noble may also serve as one fruitful point of departure for further work in developing a future unifying theory of medicine. Ultimately, systems medicine may also have to recognize that, to faithfully model a human being, it is necessary to be a human being.

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Paper II

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SCIENTIFIC CONTRIBUTION

The new holism: P4 systems medicine and the medicalization of health and life itself

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Abstract The emerging concept of systems medicine (or 'P4 medicine'—predictive, preventive, personalized and participatory) is at the vanguard of the post-genomic movement towards 'precision medicine'. It is the medical application of systems biology, the biological study of *wholes*. Of particular interest, P4 systems medicine is currently promised as a revolutionary new biomedical approach that is *holistic* rather than reductionist. This article analyzes its concept of *holism*, both with regard to methods and conceptualization of health and disease. Rather than representing a medical holism associated with basic humanistic ideas, we find a *technoscientific holism* resulting from altered technological and theoretical circumstances in biology. We argue that this holism, which is aimed at disease prevention and health optimization, points towards an expanded form of medicalization, which we call '*holistic medicalization*': Each person's whole life process is defined in biomedical, technoscientific terms as quantifiable and controllable and underlain a regime of medical control that is holistic in that it is *all-encompassing*. It is directed at all levels of functioning, from the molecular to the social, continual throughout life and aimed at managing the whole continuum from cure of disease to optimization of health. We argue that this medicalization is a very concrete materialization of a broader trend in medicine and society, which we call '*the medicalization of health and life itself*'. We explicate this holistic medicalization, discuss potential harms and conclude by calling for preventive measures aimed at avoiding eventual harmful effects of overmedicalization in systems medicine (quaternary prevention).

Keywords Biomedicalization · Holism · Medicalization · P4 medicine · Personalized medicine · Precision medicine · Primary care · Quaternary prevention · Systems biology · Systems medicine

> It is possible to get the life-phenomenon under our control … such a control and nothing else is the aim of biology—Biologist Jacques Loeb (1859–1924) (cited in Pauly 1987, p. 174).
>
> At the risk of sounding academic, you are a system. A system made up of systems, to be exact. … Our integrative—or systems—approach holistically gathers, connects, and analyzes your data to create a complete picture of you, all 360 degrees of you ... At Arivale, we don't guess. We base our recommendations—your roadmap—on your personal data story, that 360-degree view of you consisting of millions of data points.—The website of the P4 systems medicine company Arivale (2015).

Introduction

This paper is motivated by authoritative claims that medicine, and especially primary care, will soon undergo a technologically driven system change associated with

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Table 1 P4 systems medicine (predictive, preventive, personalized, participatory)

As shown by a PubMed search using the phrase '*systems medicine*', this emerging biomedical concept is in rapid growth. For the year 2008 there were seven hits. By November 2015 there were approximately 400 hits for that year
Research projects: The Institute for Systems biology (ISB) recently launched the first phase ('*The Hundred Person Wellness Project*') of its '*100 K Wellness Project*'. This is the first 'real life' clinical trial using P4SM principles. It is planned to involve quantification of a large number of parameters in 100,000 well people (Hood and Price 2014). In Europe the 'Virtual Physiological Human' and 'Digital Patient' are central research projects (Diaz et al. 2013; Hunter et al. 2013)
Clinical reality: P4SM is associated with concrete changes to clinical reality as highlighted in *the quantified self*-movement. Here individuals employ new technologies, for example genome sequencing and so-called 'eHealth', 'mHealth' or lifelogging tools (notably smart-phones) to continuously track their bodily functioning (Wolf 2009; Lupton 2014; Smarr 2012)
Institutions and companies: P4SM is associated with a range of research institutions in the USA, Europe and Asia. Systems medicine has gained support from the EU and European Commission, which have funded the 'Coordinating Action Systems Medicine' (CASyM) initiative to promote the implementation of systems medicine in Europe, as well as the Virtual Physiological Human and Digital Patient projects (Kirschner et al. 2013; Diaz et al. 2013; Hunter et al. 2013). In the USA, P4SM is strongly linked to the Institute for Systems Biology (ISB), the P4 medicine Institute (P4MI), the associated novel company Arivale. The latter has started to deliver actual health services. Another central US institution is the Harvard Medical School in Boston. In Europe, examples of central institutions are the European Institute for Systems Biology and Medicine (EISBM) in France, the Luxembourg Centre for Systems Biomedicine (LCSB), The University of Rostock, Germany and University College Dublin, Ireland. In Asia, there are institutions in India, Singapore and China, notably the Center for Systems Biomedicine in Shanghai

buzzwords such as 'genomics', 'big data', 'digital health' and 'personalized' or 'precision medicine' (ESF 2012; Topol 2012; Obama 2015). As a nexus where these developments come together we find the emerging field of *systems medicine* (see Table 1). Systems medicine is the medical application of *systems biology*, a 15-year old merger of molecular biology, mathematical modelling and systems theory (i.e. principles describing organized *wholes*) (O'Malley and Dupré 2005; De Backer et al. 2010; Bousquet et al. 2011; Green 2014). Systems medicine is often promoted as '*P4 medicine*' (*predictive, preventive, personalized* and *participatory*). We will call it '*P4 systems medicine*' ('***P4SM***').

Crucially for this contribution, P4SM is associated with promises of a '*paradigm change*' explained by the four Ps in 'P4 medicine' (Hood et al. 2012; Kirschner et al. 2013). Firstly, it promises a shift from a population-based 'one-size-fits-all' medicine to a 'personalized (or 'precision') medicine', which can account for the factors that define each particular individual (Duffy 2015). As shown in a recent textbook of personalized medicine, systems medicine overlaps with, and is having an increasing impact on, this wider concept and translational biomedical research in general (Jain 2015). Secondly, as a form of personalized medicine, it places particularly strong emphasis on shifting medicine from a focus on established disease to a prospective and proactive practice which focuses on *predictive* assessments of future health in order to facilitate disease *prevention* and *optimization* of health or wellness ('health' and 'wellness' are used synonymously here) (Diaz et al. 2013; Flores et al. 2013; Kirschner et al. 2013). Thirdly, according to its *participatory* aspect, it is promised to enable patients to shift to the role of agents driving the revolution.

Most importantly for our argument, P4SM is promised to achieve all this through a fourth change: A shift in biomedicine from a '*reductionist*' towards a '*holistic*' (or '*integrative*'[1]) approach, most vividly described by Vandamme et al. (2013):

> In the medical practice, especially in that of the general practitioner, a more holistic, systems approach has always been used. The practitioner is confronted with the patient as a whole, and focuses on their individual needs and concerns. Every physician knows that each patient is different, that there is a need for a personalization of the medical treatment that they provide. He or she constantly has to try to integrate data on the emotional state of the patient, different comorbidities, environmental factors, family history, etc. In other words, physicians deal with a lot of non-linear, multidimensional information, while the medical science they need to use to make decisions provides them with tools to make linear, reductionist decisions. There is an overall theme of 'one disease, one risk factor, one target' with a lack of dynamic information. In the coming decade, systems medicine aims to provide the tools to take into account the complexity of the human body and disease in the everyday medical practice.

Such promises of holism may seem liberating to the humanistically minded medical generalist focusing on the

[1] In systems biology the term 'integrative' may be used interchangeably with 'holistic'. 'Integrative biology' is a synonym for 'systems biology' and the moniker 'integrative healthcare' may overlap with 'systems medicine' although it is also used in alternative medicine (Jain 2015).

health of the patient as a whole. However, at the same time, P4SM is evidently based on a *technoscientific* perspective[2] that has often been at odds with such holism. As Galas and Hood (2009) state: '*Technology and new scientific strategies have always been the drivers of revolutions and this is certainly the case for P4 medicine*'.

Our perspective

The authors of this paper write from the perspective of academic general practice, specifically a Nordic welfare state where primary health care is the organizational foundation. As the point of entry to medical care, it is specifically concerned with sustainable and responsible management of the health of whole persons over time (Getz 2006). The reason why we undertake an analysis of P4SM is that it explicitly aims to revolutionize the way primary care is provided, promising to tackle a range of its challenges, including waste and iatrogenic harm. And while some of its proponents have stated that academic medicine should '*lead, follow or get out of the way*' (Snyderman and Yoediono 2008) as P4SM advances, we take a critical perspective.

Aim and material

In light of the above, we aim to analyze the concept of *holism* in P4 systems medicine, both with regard to its methods and conceptualization of health and disease. We do not pretend to assess whether this is a 'true' holism or not, but describe its contents as presented in our material and some of its implications.

As our material we have selected a set of 40 publications comprehensively outlining P4SM as it stands today. Our scope is specific for P4SM, but we do see our analysis as relevant for understanding key developments in personalized medicine and international healthcare. For more on our material and scope, see endnotes.[3,4]

Outline of the argument

Our main argument will be that P4SM aspires to make medicine holistic, yet does not entail holism as understood in what has been called *humanistic medicine*, a stream of medical thought and practice which focuses on the functioning, subjective experience and values of patients as whole persons, and which is frequently associated with an anti-medicalization

[2] In this article the term '*technoscientific*' is used broadly to refer to any phenomenon that is at once scientific and strongly linked to technology.

[3] This article is part of a larger project investigating P4SM as a proposed framework for primary care, and as such it is based on a thorough research into the subject matter and underlying philosophical issues involving many literature searches. To delineate a suitable and transparent material for this analysis, we performed the following PubMed search: '"systems medicine" OR "systems biomedicine" OR "P4 medicine" OR "4P medicine"'. Last performed 2015-11-23 this search yielded 1623 hits. We focused on identifying comprehensive, theoretical publications outlining P4SM that are broad in scope and especially relevant for understanding P4SM as a framework for primary care. We excluded shorter publications (e.g. editorials) and publications focusing on particular medical problems or specialities. We thereby selected 31 publications, the oldest from 2008. We see this material as reflecting the emerging field of P4SM well. As described by other authors, systems biology may be divided in different schools (O'Malley and Dupré 2005; De Backer et al. 2010; Thomas 2007). The dominant "pragmatic" or "molecular" school is rooted in functional genomics and has traditionally sought network-based explanations at the cellular level using high-throughput 'omics' data. There is also a school rooted in traditional physiology, which is more focused on models connecting all biological levels. A 'systems-theoretical' school describes researchers that focus strongly on systems theory principles. These schools are now merging and all are reflected in our material. However, it suitably mostly reflects the dominant school. The most influential research environment here is located at The Institute for systems biology (ISB) in Seattle, USA. Its leading figure, Leroy Hood, is represented in 10 of the 31 initial publications. Seeing its '*Hundred Person Wellness Project*' (see Table 1) as especially relevant for our article, we searched the ISB's list of publications and annual reports at www.systemsbiology.org and identified 5 additional publications. Based on our research (reading of reference lists etc.) we also identified and included an early online document, a European 'Roadmap to Systems medicine', a European 'Digital Patient Roadmap' as well as a strategy publication for the Virtual physiological human (Hood and Galas 2008; Kirschner et al. 2013; Hunter et al. 2013; Diaz et al. 2013). The latter two are representative of the 'physiological' school of systems medicine. In sum, we included 40 publications, all identified in our reference list.

[4] P4SM cannot be seen as representative of biomedicine at large. However, it is relevant for understanding of broad developments in international healthcare. Recent remarks made by US president Barack Obama announcing the Precision Medicine Initiative may serve as an example (Obama 2015): "*The (…) human genome (…) today (…) costs less than $2000. Wearable electronics make it easier than ever to record vital signs (…) And more powerful computers help us analyze data faster than ever before. So if we combine all these emerging technologies, if we focus them and make sure that the connections are made (…) the possibilities are boundless*.' Obama also emphasised participatory medicine ('*…we want every American ultimately to be able to securely access and analyze their own health data, so that they can make the best decisions for themselves and for their families*'). As another example, British Secretary of Health, James Hunt, recently declared: '*If you talk to technology gurus in California (…) They say "You can get three hundred thousand biomarkers from a single drop of blood, so why would you depend on a human brain to calculate what that means when a computer can do it for you*? *(…) I think it's really important that we're ready in the NHS to harness the power of data to give us more accurate diagnoses (…) What this will mean, is we can identify problems before they're symptomatic and therefore have a much better chance of tackling them*' (Matthews-King 2015). These comments are related to the ideas of P4SM. Moreover, one may note that professor Eric Topol, author of the '*The Creative Destruction of medicine*', is in the scientific advisory board at the P4SM company Arivale (see Table 1). P4SM also influences US academic medicine (Snyderman and Yoediono 2008).

stance (Engel 1977; Marcum 2008; McWhinney and Freeman 2009; Cassell 2013; Miles 2013). Contrary to this position, we observe how P4SM represents a *technoscientific holism* resulting from an altered, more all-encompassing technological gaze on human life and related changes in biomedicine's methods and philosophy. We then argue that this form of holism points towards an expanded form of medicalization, which we call *holistic medicalization*: Each person's whole dynamic life process is defined in biomedical, technoscientific terms as controllable and underlain a regime of control in terms of monitoring, quantification, prediction, risk profiling, early diagnosis, therapy, prevention and optimization that is *all-encompassing*. By 'all-encompassing' (which here corresponds to the term 'holistic') we mean *multi-dimensional, continual throughout life* as well as *directed at controlling all types of functioning, primarily healthy life*.

We do not by this pretend to discover an entirely new development. Rather, we argue that this expanded medicalization can be seen as the hitherto most concrete and comprehensive materialization of a broader trend, which has previously been described by several theorists and concepts. We will especially rely on three of these: *biohealth, biomedicalization and biopolitics* (Rose 2007; Clarke et al. 2010; Downing 2011). From our generalist point of view we see these concepts as closely related and refer to the historical development that they together describe as '*the medicalization of health and life itself*'. We here define *medicalization* very generally as *the process by which aspects of human life come to be defined in medical terms and underlain medical control* (Conrad 2007). We do not see this process as driven solely by medicine, but by many agents.

In the following, we will detail the above exposition in three parts. (1) In the first part, consisting of the sections 'A technoscientific holism' and 'Health in technoscientific holism', we show how the holism of P4SM arises from an interaction between theoretical and technological circumstances and specify how it defines health, disease and 'life itself'. With regard to our argument, the main picture that emerges is that—however complex—these phenomena are rendered potentially *knowable* and *controllable* by biomedicine. (2) In the second part, consisting of the sections 'Holistic medicalization', 'Holistic medicalization in practice' and 'Participatory medicalization' we then spell out how this technoscientific holism points towards a *holistic medicalization*. (3) We then discuss implicated 'Potential waste and harm'.

A technoscientific holism

A 'holistic' solution for biocomplexity

Aiming to analyze the meaning of '*holism*' in P4 systems medicine, we will first explicate the historical context in which systems biologists use this term. In large part this is to contrast their approach to a personalized medicine based on the methods of molecular biology (Calvert and Fujimura 2009).

During the twentieth century there was always a stream of thought in biology stressing that living organisms are *more than the sum of their parts* and should be studied as integrated systems or *wholes* (Gilbert and Sarkar 2000). However, as tools for the scientific, empirical study of such wholes were largely unavailable, this *holism* was sidelined by the '*divide and conquer*' strategy of molecular biology. Molecular biology can be said to have been '*reductionist*' in that it was limited to focusing on one or a few, isolated bodily parts and relatively simple or *linear* causal relationships between parts (especially DNA) and the whole (health and disease). However, some 15 years after the sequencing of the human genome—molecular biology's flagship project, culminating around the year 2000—this view is in crisis. Increasing empirical evidence has underscored that this genotype–phenotype relationship is more *complex* or *non-linear* than assumed (Woese 2004; Keller 2005). Systems medicine, which partly springs out of the human genome project and functional genomics, reflects this realization: In order to understand, predict—and thus *control*—the complexity of health and disease, one must study these phenomena in terms of integrated, dynamic, *complex systems* (Thomas 2007; Auffray et al. 2009; Antony et al. 2012; Wang et al. 2015). Systems medicine thus offers a solution to the challenge of biocomplexity that its proponents describe as '*holistic*'. Quote systems biologist Leroy Hood (2008):

> The dominant challenge for all the scientific and engineering disciplines in the twenty-first century will be complexity, and biology is now in a unique position to solve the deep problems arising from its complexity and to begin to apply this knowledge to the most challenging issues of humankind. Biology will use systems approaches (holistic, as opposed to atomistic) and powerful new measurement and visualization technologies, as well as the new computational and mathematical tools that are emerging in the aftermath of the human genome project and the emergence of systems biology.

As indicated by this statement, a crucial enabling factor behind the holism of P4SM is new technology. These tools constrain the questions it may ask empirically. Crucially for our argument they also enable continued hope that, however complex, human wholes may yet be defined and controlled by science.

A holistic method

Hood and Flores (2012) summarize the method of P4SM as follows:

> Ironically many people use the term 'genomic medicine' to denote the medicine of the future—yet in principle genomic medicine is one-dimensional in nature—only encompassing nucleic acid information. Systems medicine, by contrast, is holistic and utilizes all types of biological information—DNA, RNA, protein, metabolites, small molecules, interactions, cells, organs, individuals, social networks and external environmental signals—integrating them so as to lead to predictive and actionable models for health and disease.

As exemplified by the above quotation, proponents of P4SM use the term 'holistic' in two related ways with regard to their methods and tools:

1. '*Holistic measurements*': Firstly, the word '*holistic*' comes to mean the use of new technologies to gather *big data* about each particular person that are as *all-encompassing* or '*global*' as possible (De Backer et al. 2010; Diaz et al. 2013; Flores et al. 2013). These measurements in turn have two aspects that will reappear in what we call *holistic medicalization*: (a) Spatially, the measurements are *multi-dimensional* in that they pertain to all levels of biological organization. (b) Temporally, the technologies enable *repeated* or *continual* measurements through time that represent the dynamism of health and disease in a way that is new to biomedicine (Emmert-Streib and Dehmer 2013). The envisioned end result is a dynamic data cloud that reflects *the whole life process* in all four dimensions, consisting of '*billions of data points*' (Bousquet et al. 2011).
   All conceivable technologies could potentially contribute to these measurements. However, the core data are molecular and enabled by new, high-throughput '*omics*' technologies that generate whole '*parts lists*' of molecules (e.g. genomics, proteomics, transcriptomics, metabolomics, epigenomics) (Ayers and Day 2015; Wang et al. 2015). Additionally, a massive phenotyping ('phenomics') and mapping of environmental exposures is undertaken using for example microbiomics of bacterial flora, imaging, electronic health records, home telemonitoring, social media and various sensor technologies (implanted or external) coupled to smart-phones to monitor a range of bodily functions (Diaz et al. 2013).
2. '*Holistic (integrative) models*': Secondly, the '*holistic*' method involves using novel computer technologies to interpret the initially fragmented '*holistic data*'. One set of methods in this sense-making process comes from bioinformatics, but the key objective of systems medicine is to use mathematical modelling to *integrate* the data in what is called '*holistic multi-scale models*' (Duffy 2015, see also Clermont et al. 2009; Wolkenhauer et al. 2014). According to Flores et al. (2013), '*These models decipher biological complexity by showing how all elements in biological systems interact with each other to produce health and disease states*'. A main goal is to study the way bodily systems transition between health and disease and thus generate the mechanistic explanations and predictive power needed to establish control of complex wholes (Hood and Price 2014). Crucially, the technologies of P4SM now also allow monitoring of the phases of life in which people are healthy, enabling nothing less than an attempt to *quantify health* (Hood 2013). This may be seen as an aspect of systems biology's wider aim of *calculating life*, as expressed by Boogerd et al. (2007, chapter 14): '*With systems biology, life, first at the simplest level (…) and perhaps ultimately at the level of intelligent human beings will become calculable*'. Perhaps the ultimate expression of the goal of quantifying the whole life process is the European *Digital Patient* project, which aims to create a '*medical avatar*' of each citizen to be compared to a generic '*virtual physiological human*' (Hunter et al. 2013). According to its roadmap, '*Avatar literally means embodiment or manifestation and is a 4D personalised representation of individual patients*' that can '*provide individualised (person-specific) future projections, systemic predictions based on mechanistic understanding of the disease process in an integrative and holistic view*' (Diaz et al. 2013, p. 60 and p. 13).

Holistic theory

On the theoretical level, the holism of P4SM corresponds to the idea of life as a complex system, which by definition refers to some kind of integrated whole. However, how a '*system*' (and the *emergent properties* that arise from its dynamics) are understood may in turn vary, making different 'holisms' possible (O'Malley and Dupré 2005). Systems theory could potentially be used to argue that human health is so complex that it is hard to predict and control[5] (Bishop 2011). However, in practice, the models

[5] Here it seems pertinent to note that, in the past, representatives of humanistic medicine have also employed systems theory in their holistic conceptions of health, but then mainly to bolster an emphasis on the social interactions and personal experience of human wholes (Engel 1977; McWhinney and Freeman 2009; Sturmberg 2013).

that define P4SM theory seem mostly to be chosen with the aim of controlling the workings of wholes. As Tian et al. (2012) clearly state: '*Models may be descriptive, graphical or mathematical as dictated by the amount of available data, but they must be predictive. For medical use, predictions made must be actionable and useful for treating patients*'.

For this purpose models are mainly adopted from mathematics, physics, computer science and engineering (Antony et al. 2012; Hunter et al. 2013; Wolkenhauer et al. 2013; Wang et al. 2015). Moreno et al. (2011) describe this systems theory or '*network theory*', as…

> …the set of mathematical and computer simulation models and tools that have been developed to study network architectures and dynamics. Although there is no unified branch or corpus of mathematics that constitutes network theory, there exists however an increasingly indispensable 'tool-kit' of methods and disciplines that merge into what we might call network theory: this ranges from dynamical systems theory to network topology, from random boolean network models to coupled oscillators. The study of networks with strongly and recurrently interacting components allowed scientists to deal with holistic systems, showing that, despite their variety, they share certain generic properties.

In sum, we see a radically expanded approach to studying human beings.

Health in technoscientific holism

This *technoscientific holism* alters biomedicine's conception of health and disease ('*the biomedical model*') in several ways:

Health as multi-level

In P4SM technology and theory now allow health and disease to be characterized as multi-level phenomena. The whole human organism is portrayed as a highly non-linear system, often as a *network of networks* (Hood et al. 2012; Vandamme et al. 2013) (see Figs. 1, 2). P4SM thus takes biomedicine from conceptualizing health and disease as resulting from *linear relationships* between parts and wholes (a '*gene-centric*' view) to a multi-causal, non-linear '*network-centric*' view (Younesi and Hofmann-Apitius 2013).

Health as process

Relatedly, P4SM's longitudinal monitoring and theories of system dynamics promote a *process view* of health, taking biomedicine along an epistemological '*epigenetic turn*' (Nicolosi and Ruivenkamp 2012). The development of each individual is conceptualized as the process of *gene–environment interaction (GxE),* where the '*environment*' includes 'psychosocial' factors. Crucially, these interactions may be seen as genetic and environmental *information* that is integrated and encoded in the dynamic networks. To some systems biologists, biomedicine then becomes the informational science that deciphers this information (Bousquet et al. 2011).

Health and disease as system states

This leads us to the P4SM definition of health and disease. Both phenomena are conceptualized as dynamic, functional *states* of the system that emerge through the GxE process (del Sol et al. 2010; Bousquet et al. 2011). These states may be seen as *emergent properties* of the whole, and health may also be conceptualized as *robustness* (the ability to maintain system integrity despite perturbations) (Federoff and Gostin 2009; Antony et al. 2012). In this picture, health and disease may also be seen as different aspects of a single *continuum* of potential network states in space and time (Hood and Flores 2012). Diseases may be defined in terms of *abnormal* and health in minimal terms as *normal network states* (del Sol et al. 2010) (see Fig. 2). The totality of possible states a system can be in is defined as a '*state space*', and health and disease as different trajectories of states in this space (Antony et al. 2012).

Health as individual specific

As the interactions between environmental and genetic factors are quite unique in each particular case, health and disease are underscored as individual-specific phenomena in P4SM. Technologies describing each individual in detail support this view. According to Bousquet et al. (2011), non-communicable diseases '*should be considered as the expression of a continuum or common group of diseases with intertwined gene–environment, socio-economic interactions and co-morbidities that lead to complex phenotypes specific for each individual.*'

A mechanistic and predictable health

So far, we have described the factors that make the P4SM conception of health '*holistic*'. What qualifies this holism as '*technoscientific*'?

Systems biology is the site of deep epistemological and ontological discussions, notably about causation and predictability in living organisms (Wolkenhauer et al. 2013; Wolkenhauer and Green 2013; Boissel et al. 2015). However, mainstream P4SM seems to adhere to the machine

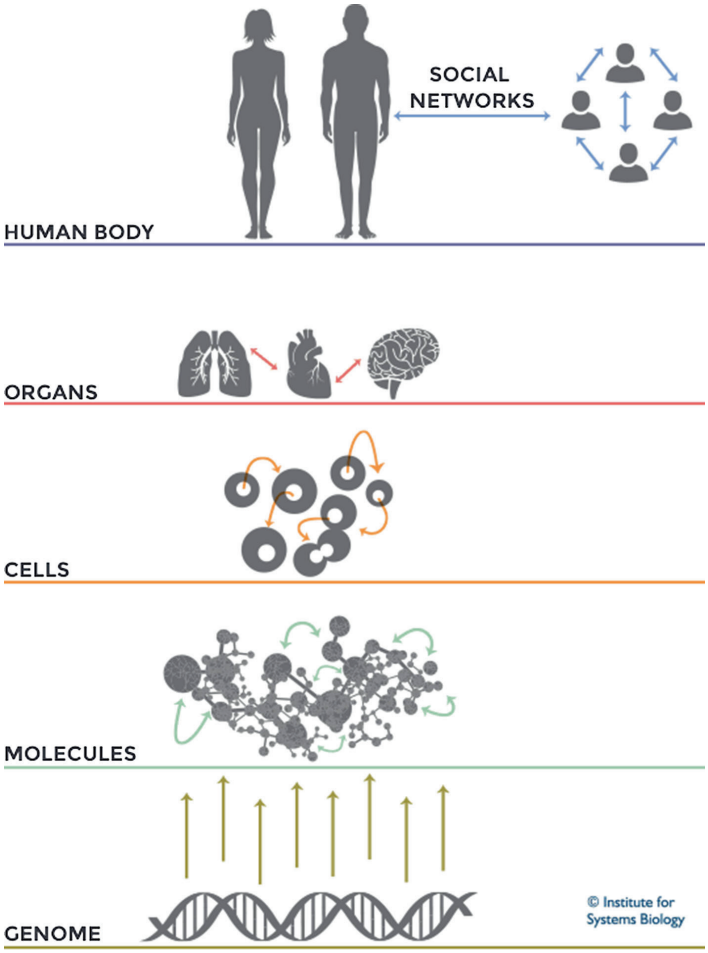

Fig. 1 The human being as a dynamic network of networks. In systems medicine the human organism is envisioned as a system of systems or *network of networks*. At every scale of biological organization (molecular, cellular, organ, individual and social/environmental) systems are portrayed as giving rise to and embedding each other. At all levels the network of networks is seen as a dynamic or four-dimensional process (as opposed to a static thing) (Copyright: The Institute for Systems Biology, used with permission)

metaphor of life. Mechanistic explanation and predictive power are main goals. Its mathematical models are often mechanistic and deterministic, and health and disease are widely defined as *mechanistically explainable*.[6] Most significantly for our argument, the whole and its health are defined as potentially quantifiable (Antony et al. 2012; Diaz et al. 2013; Flores et al. 2013; Kirschner et al. 2013; Cesario et al. 2014b; Wang et al. 2015). In P4SM—as in systems biology—the concept of *holism* seems often to go hand in hand with the assumption that the emergent properties of the whole (i.e. health or illness) can be mechanistically explained and scientifically predicted (Boogerd et al. 2007). P4SM attempts to describe the unfolding process in mechanistic detail as something *concrete* (Boenink 2009). Consider Fig. 2: Represented in a technologically generated virtual reality, it is as if health and disease are objective and *there*. And while the metaphor of the genome as the '*book of life*' may be obsolete, and the road towards unravelling the actual mechanistic

[6] A radio analogy of life has been frequently used in systems biology. Leroy Hood brings it to systems medicine: '*A holistic, integrative or systems approach can be explained by a simple analogy. In order to understand how a radio converts electromagnetic waves into sound waves, the first step would be to compile a list of its components. Then the components would be studied individually to ascertain what each component does independently. After understanding the individual parts, the next step would be to assemble the parts into circuits and then understand individually and collectively how the circuits convert radio waves into sound waves*' (Hood 2013).

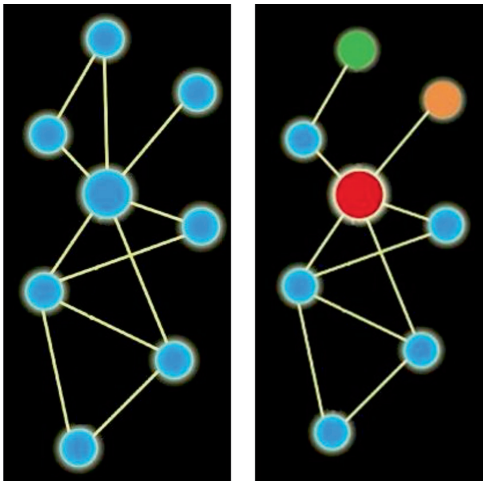

Fig. 2 Disease and health as network states. One common way to represent systems or networks in PMSM is as *graphs*, where interacting units (e.g. molecules) are *nodes* and their interactions *edges*. According to one publication, this figure presents 'A schematic view of a normal (*left*) and a disease-perturbed network (*right*). Both node points (*colored balls*) and edges (*lines attaching the balls*) change in disease as indicated by changing colors indicative of changing levels and the disappearance of an edge. The nodes and edges change dynamically with disease progression' (Hood 2013). (Copyright: The Institute for Systems Biology, used with permission). (Color figure online)

workings of the body long, the whole life story may still be portrayed as *information* that biomedicine can decipher (Bousquet et al. 2011).

The most striking example of the idea of life as calculable is a programmatic proposition by leading figures to '*generate a multiparameter metric for wellness—by employing data from individuals exhibiting wellness over an extended period of time. It will reflect both the psychological and physiological aspects of wellness*' (Hood et al. 2015a). According to Cesario et al. (2014b), '*Wellness as a status to be achieved and maintained in our lives, getting longer and hopefully healtier, is the new and comprehensive declination of "health" itself, leading the shaping of research and research policy in the health domain worldwide.*' Flores et al. (2013) even state that P4SM models will be '*increasingly powerful predictors of each individual's personal experience of health and disease. These models not only demystify disease, they also quantify what it means to be healthy*'.

All in all, the picture that emerges in P4SM is an effort to make medicine a *harder science* (Calvert and Fujimura 2009). It is a holism that entails a strong form of *naturalism*, which, in a medical context, is the view that health and disease are knowable through the methods of natural science (Marcum 2008).

A controllable health

This naturalism is philosophically attractive: It appears to render not only disease but also states of wellness potentially *controllable*. Quote Hood and Flores (2012): '*Systems (P4) medicine is now pioneering something that never existed before—actionable understandings of disease and wellness as a continuum of network states, unique in time and space to each individual human being*'.

On the theoretical level, this is the essence of technoscientific holism: Although the whole life process of each individual is defined as complex, this whole—and the whole continuum of health and disease states it may be in—is defined as potentially quantifiable, predictable and *actionable*. 'Actionable' here means *controllable*. And defining an aspect of life in medical terms as controllable is a key step in the process of *medicalization*, leading us to the second main part of our argument (Conrad 2007).

Holistic medicalization

We will now spell out how we see *technoscientific holism* as pointing towards a *holistic medicalization*. We begin by outlining the wider trend in which we place this development: '*the medicalization of health and life itself*'.

The medicalization of health and life itself

Somewhat simplified, we can say that biomedicine, with its technoscientific approach, has traditionally been limited to a reactive and reductionist focus on parts-associated disease. As a corollary, biomedically rooted medicalization has mostly consisted in labelling aspects of life *as diseases*. Healthy life has largely been dismissed as *the absence of disease* (Hofmann 2002; Marcum 2008). In other words, our path towards health itself has not been medicalized by technoscientific biomedicine like our approach to suffering.

The biomedical focus on disease has left an open space for attention to wholeness, health and human life-stories. Alternative medicine aside, this space has most often been filled by the holism of what has been called *humanistic medicine* (Marcum 2008). Such holism has been most strongly associated with medical generalism and concepts such as biopsychosocial, patient-centered, person-centered and narrative medicine (Engel 1977; McWhinney and Freeman 2009; Cassell 2013; Miles 2013). Traditionally, it is also this stream of thought that has advocated a shift in focus from disease towards the concept of health or well-being (Cassell 2013). Such holism has then typically linked

health to capacities of *the whole person* as a conscious agent and tended to define these capacities as beyond exact scientific description. Instead, health has been tied to the most complex aspects of human life and thought to be a subjective and culturally value-laden (normative) phenomenon (Boenink 2009; Sturmberg 2013). Health has thereby been defined in positive terms as something *more and other than the absence of disease* that may even be *compatible with disease.* Critically, this form of holism has been associated with a certain tolerance towards disease and death and skepticism towards medicalization. Health has simply not been considered technoscientifically actionable like disease (Gadamer 1996; Hofmann 2002).

This traditional state of affairs is undergoing deep change through 'the *medicalization of health and life itself*' as described by three concepts: *biohealth*, *biomedicalization* and *biopolitics* (Rose 2007; Clarke et al. 2010; Downing 2011). With P4SM the undercurrents that these authors have pointed at seem to surface as a comprehensive framework.

Biohealth, biomedicalization, biopolitics

Primary care physician and philosopher Raymond Downing describes his concept of *biohealth* as follows:

> We are now in a phase beyond medicalization when even health—the "opposite" of medicine's focus, disease—has become medicalized. Biomedicine, assuming it knows what health is, imposes that understanding on everyone. Medicine used to claim authority over the cracks and interruptions in life; now it claims authority over all of life (Downing 2011, p. 2).

According to Downing systems thinking inherently leads to an expansion of medicalization as it induces us to capture *all aspects* of a phenomenon (e.g. a person's life). And: '*In describing or designing a system, we not only want to include every part, we also want to make each part captive, to control it*' (Downing 2011, p. 70). Medicalization may in fact be seen as an inbuilt potential of all holism as holism is, by definition, *all-encompassing.*[7]

[7] Downing also directs the criticism that systems thinking leads to medicalization towards the use of systems theory in Engel's biopsychosocial model and patient-centered medicine (Engel 1977; McWhinney and Freeman 2009). However, we see important differences between this and P4SM. The adoption of systems theory in what has been called *humanistic medicine* has been intended as a metaphorical tool when one competent clinician seeks to 'model' other persons in order to avoid reducing their problems to molecules. In P4SM, such 'human modelling' would be replaced mathematical modelling and the doctor-patient relationship with a computer interface and computational decision support.

Similarly to *biohealth*, the concept of '*biomedicalization*', developed by sociologist Adele Clarke and coworkers, describes an expansion of medicalization: A broad, multi-faceted trend towards not only defining and controlling evermore aspects of life *as disease*, but increasingly also towards *health optimization* and '*The extension of medical jurisdiction over health itself (in addition to illness, disease and injury*)' (Clarke et al. 2010, p. 48).

Biopolitics (the term 'politics' connoting 'power') is a perspective developed by sociologist Nikolas Rose, building on philosopher Michel Foucault's concept of *biopower*. It refers to *a management of life*, which…

> …is neither delimited by the poles of illness and health, nor focused on eliminating pathology to protect the destiny of the nation. Rather, it is concerned with our growing capacities to control, manage, engineer, reshape, and modulate the very vital capacities of human beings as living creatures. It is, I suggest a politics of "life itself" (Rose 2007, p. 3).

Holistic medicalization in theory

How does medicalization become '*holistic*' on a theoretical level in P4SM; how does it *define aspects of life in medical terms*? Although this is not the place to enter the vast debates on health and holism, we first want to note that the concepts of *holism*, *wholes, wholeness* and *health* are etymologically and philosophically related. The very foundation of these ideas is now changing. '*Biohealth*', Downing remarks is '*the sort of health and wholeness that results from applying the biological sciences*' (Downing 2011, p. 6).

We will argue that the '*holistic medicalization*' of P4SM is envisioned as the most advanced and systematic example to date of what Downing is pointing at. As we hope to have shown, the very idea of holism is redefined in P4SM and given a technoscientific meaning. In other words, the aspect of life that is defined in medical terms is *wholeness itself*. When the life process is understood in terms of dynamic wholes, but these wholes are defined as quantifiable and controllable through technoscientific means, biomedicalization becomes holistic on a theoretical level. *Holistic medicalization* does not primarily entail that aspects of life are defined *as new diseases*. Rather, it puts wholeness and health itself under medical jurisdiction, pointing toward a situation in which 'life itself' is controlled.

This is highlighted by the idea that one can provide *a multi-level metric for wellness*, with not only '*physiological*', but also '*psychological*' parameters by which to orient one's way of life. According to this view, health is '*a concept that to date has been defined in vague and*

ambiguous terms' (Hood et al. 2015a). Through *techno-scientific holism* this '*vagueness*' is now to come to an end. As scientists at the Institute for Systems Biology state, '*wellness—and how to enhance it and extend it—has not been studied very thoroughly by scientists. ISB proposes to change this by taking a systems-approach to understanding wellness—and thereby make it scientific*' (Hood et al. 2015b). This idea of a '*scientific wellness*' becomes even more radical as the disease-health continuum should—at least according to Hood and coauthors—not be envisioned as stopping at *normality*, but as additionally involving a positive '*wellness space*' of network states that is *more and other* than absence of disease (Flores et al. 2013). However, in sharp contrast to humanistic medical holism, see e.g. Cassell (2013), this positively defined health is portrayed as something that can be defined through techno-scientific means.

From molecularization towards synthesis

An important claim in the concepts of *biomedicalization* and *biopolitics* is that health and 'life itself' have increasingly become *molecularized* (Rose 2007; Clarke et al. 2010). Rose remarks that '*It is now at the molecular level that human life is understood, at the molecular level that its processes can be anatomized, and at the molecular level that life can now be engineered*' (Rose 2007, p. 4). Does the holism of P4SM also involve such *molecularization*? The answer is '*yes, but*…'.

Systems biology is technologically strongly focused on molecular parts (De Backer et al. 2010). As a corollary the wholes that P4SM models are also mostly *molecular wholes* (Mardinoglu and Nielsen 2012; Emmert-Streib and Dehmer 2013; Ayers and Day 2015; Wang et al. 2015). As illustrated by talk of '*molecular level (…) processes that define and drive physiology*' and provide '*deep understanding of causality*' (Flores et al. 2013), the molecular is central to its philosophy of causation and epistemology. The overall aim is to connect the whole to its parts, and the whole seems mostly to be defined *in molecular terms*. Such a *molecular holism* is a contradiction in terms and better understood as a form of *reductionism* (De Backer et al. 2010).

However, at the same time, P4SM involves profound discussions about the organizing principles by which wholes govern parts (Antony et al. 2012; Wolkenhauer et al. 2013; Wolkenhauer and Green 2013). Its deepest theoretical contribution may be that it slowly moves biomedicine from a one-dimensional molecular focus towards a view where no level is causally or epistemologically privileged (Noble 2007; O'Malley and Dupré 2005). Quote Boissel et al. (2015): '*The solution must include multilevel interactions in an integrative approach. Thus, systems medicine should go beyond the realm of the intracellular layer to integrate upper physiological layers, including all time and complexity level components*'.

This seems partly at odds with Rose's view of molecularization as an epistemological change away from the nineteenth century view of the body as a '*system of systems*' (Rose 2007, p. 43). P4SM represents precisely a move towards such a view. Our key point in this article is that this also changes medicalization. As new tools now seem to allow synthesis, the process of medicalization also moves beyond molecularization to a *synthetic phase*. The endgame of medicalization will result from trying to piece all bodily pieces together to define and control life *in toto*.

Defining the limits of medicalization

In one publication, Juengst et al. (2012) voiced concerns over potential problems with personalized medicine—for example pursuit of human enhancement. P4SM proponents responded by pointing precisely to their *holism*:

> For the most part, these concerns are alleviated by eliminating the undue focus on genetics (…), the scientific and technological foundation of P4 healthcare rests on systems approaches to big data on many different dimensions of health, not just genomic factors. Systems approaches are powerful precisely because they integrate all of these data to delineate how environmental and genetic factors interact to shape individual experiences of health and disease (Flores et al. 2013).

However, to the extent that medicalization poses problems, this argument offers cold comfort. For the more *holistic* P4SM will become, while at the same time defining '*the whole*' as technoscientifically actionable, the more medicalizing it may get. The perfect endgame, a technologically based mirror image—or '*avatar*'—of each individual that enables the prediction and control of all health aspects—will logically also involve *total medicalization*. We conjecture that systems medicine will define the future limits of medicalization. As the major rate-limiting hindrance to medicalization is biocomplexity, and P4SM models will likely define biomedicine's uttermost efforts to overcome this complexity, it will also delineate the degree to which life can be technoscientifically controlled.

Holistic medicalization in practice

What would holistic medicalization of P4SM look like in practice, if realized? A vision presented in the European '*Digital Patient*' roadmap is illuminating:

> The vision of a "digital me" that contains all my health-care information, (…) communicated with all my wearable and implanted technology to constantly monitor my health status and informing me, my family and friends, or my healthcare providers of alarming events, supporting the collaboration of various specialists around my complex systemic diseases, and used with all my data to predict the future development of my health in order to facilitate disease prevention and a fully self-aware lifestyle (Diaz et al. 2013, p. 57).

Firstly, we see that P4SM would still be directed at managing disease, especially chronic disease that requires long-term management of life (Cesario et al. 2014a). However, while disease would still be one focus, healthcare would shift in scope so as to favour the management of the health and lives of healthy or asymptomatic people—that is *all people.* This management would be both multi-level, continuous throughout the lifecourse and directed at all types of network states all along the continuum from overt pathology, via more or less well-discerned risk profiles, 'normality' and into the positive '*wellness space*' (Diaz et al. 2013; Flores et al. 2013).

The main thrust in P4SM would be *prevention* involving risk profiling and early diagnosis in healthy or asymptomatic people (Bousquet et al. 2011). The definition of health as potentially predictable and controllable may be key to this ambition:

> In the future, we will be able to design drugs to prevent networks from becoming disease perturbed. For example, if there is an 80 % change of prostate cancer at age 50, taking these preventive drugs beginning at age 35 may reduce disease probability to 2 % (Hood 2008).

In addition to disease management and prevention, P4SM practice would—at least according to some leading proponents—not only be directed at disease as something negative, but *optimization* of *health* or *wellness* as something positive. Another 'P' could thereby be added to 'P4': Promotive medicine. According to Boissel et al. (2015), '*The optimization of wellness is a key to maximizing human potential for each individual—improving physiological as well as psychological performances.*'

With regard to such optimization, one key aim is to elucidate and manipulate the process of ageing, which is hard to delineate from the process of 'life itself' (Hood and Flores 2012; Bousquet et al. 2014). As an example, the *Digital Patient Roadmap* reduces aging to the dominant risk factor of disease: '*Ageing is a hurdle to overcome and its inclusion is personalised models for the Digital Patient is a challenge that multi-scale models will need to resolve*' (Diaz et al. 2013). Even more profoundly, systems biology is also the basis of *synthetic biology*, which aims specifically to engineer new properties of life (Auffray et al. 2009).

Optimization or *enhancement* of human capacities is central to the concepts of *biohealth, biomedicalization* and *biopolitics* (i.e. the' medicalization of health and life itself'). According to Rose, '*The old lines between treatment, correction, and enhancement can no longer be sustained*' (Rose 2007, p. 6). When P4SM becomes sufficiently efficient in transforming the processes of life, these borders will blur. In the P4SM visions, prevention also seems based on optimization, and optimization always to imply that something is in some way *suboptimal*. It also seems clear that the proposed P4SM metrics of health will involve many of the same (predominantly molecular) parameters used to define disease (Wang et al. 2010). If so, the language of health will to a large extent be derived from the language of disease.

Diagnostics and prognostics

As part of a preventive and health-optimization strategy, diagnostics and prognostics would as default involve a multi-level, continuous and individualized monitoring or *screening process* (Bousquet et al. 2011). This amounts to an advanced form of what has been called *surveillance medicine* (Armstrong 1995). Although the diagnostic process would use information from all levels in a 'holistic' fashion, it would be biomarker-based (Mardinoglu and Nielsen 2012; Younesi and Hofmann-Apitius 2013). And while previous biomarkers have mostly been single-component, future P4SM biomarkers may be '*network biomarkers*' (Wang et al. 2015). One aim is to make '*blood a window for assessing health and disease*' (Hood and Flores 2012) by constructing diagnostic technologies that can regularly assess '*molecular fingerprints*' reflecting specific network states (Wang et al. 2010).

Risk is a key concept in *the medicalization of health and 'life itself'* (Clarke et al. 2010; Downing 2011; Rose 2007). With regard to disease prevention, we conjecture that the very concepts of risk or susceptibility to disease will change in P4SM. As the idea of what holds our destiny changes from static DNA or a few riskfactors to the workings of the dynamic network, they will become more multi-factorial and dynamic concepts. The need to account for all these factors implies a increased focus on risk that is unprecedented in its all-encompassing scope.

If P4SM would venture into active health optimization, '*actionable possibilities*' would additionally emerge in positive *wellness space*—pointing perhaps towards a radically new *diagnostics of health* (Hood and Price 2014). Preliminary results from the ISB '*Hundred Person*

Wellness Project' show how expansive P4SM may become in labelling well people: '*So far, after having analyzed just a few types of data, we've found that 100 % of the 100 Pioneers have multiple actionable possibilities*' (Hood 2014). Here, the concept of 'an actionable', frequently used by Hood and collegues, may both be understood as a relabelling of the traditional concept of risk of disease, but also as a piece of information that may be useful in enhancing one's wellness or performance.

Intervention

Like the diagnostic process, intervention would also turn into a life-long, dynamic project that would be directed at tackling all components of the complexity of health, including potentially the personal (or 'psychological') and social. A large group of P4SM advocates argues that management of non-communicable disease (NCD)…

> …should move towards holistic multi-modal integrated care, and multi-scale, multi-level systems approaches. (…) Systems medicine aims to tackle all components of the complexity of NCDs so as to understand these various phenotypes and hence enable prevention (Bousquet et al. 2011).

Genes are no longer regarded as destiny. As a corollary, P4SM emphasises preventive lifestyle interventions (Bousquet et al. 2014; Hood 2014). In this regard, what is considered 'medical treatment' might potentially change and focus more on non-technological intervention. This may also seem *non-medicalizing*. However, biomedicine would still strengthen its grip on what it means to lead a healthy life, and even lifestyle, living itself, would be grounded in a continuous, technologically based monitoring of risk-factors.

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. Drug development is a main focus: '*By deciphering which biological networks are perturbed in diseases, systems medicine will provide a stream of new drug targets for the pharmaceutical industry*' (Flores et al. 2013). In accordance with the principles of network theory, pharmaceutical intervention would also change, turning into a process of control engineering. As the view of what must be controlled changes from linear to non-linear, treatment is also envisioned as multicausal: '*A new "network-centric" rather than "gene-centric" approach to choosing drug targets will employ multiple drugs to "re-engineer" a disease-perturbed network to make it behave in a more normal manner*' (Hood and Flores 2012). In other words, technoscientific holism leads to a complexification of pharmaceutical treatment and polypharmacy as default.

Participatory medicalization

According to its *participatory* aspect, P4SM is envisioned as requiring an expansion of healthcare far beyond the clinic. Patients, families and communities working in networks are expected to drive its realization (Diaz et al. 2013; Hood and Auffray 2013; Kirschner et al. 2013). As this aspect defines P4SM, it will also define an aspect of *holistic medicalization*. We will call this *participatory medicalization*.

Again the novel technologies of P4SM are the enabling factor. Firstly, they are primarily directed at the individual body and its subsystems. Correspondingly, both personal *and* public health is tied to the individual person, who is expected to live life to the fullest in symbiosis with the biomedical tools that provide access to health. The longitudinal cloud of billions of data points gathered for each individual allows his/her life to be envisioned as a form of *N-of-1 study* in which each person is a vital participant in his or her own 'holistic' description (Kirschner et al. 2013; Hood and Price 2014). This is one hallmark of 'the medicalization of health and life itself': It is focused on the individual and health becomes a personal goal and responsibility (Rose 2007; Clarke et al. 2010; Downing 2011).

Secondly, the quest for *personalized* medicine (somewhat paradoxically) requires *everyone* to participate. To develop valid predictive power, P4SM needs data from a population that is as big and diverse as possible in order to mine the data for regularities, to demarcate health and to stratify the population:

> In order to take into account the full range of biological complexity and define the range of healthy behavior, these data need to be obtained for as many people as possible in the population—ideally everyone—not just for small test samples (Flores et al. 2013).

This need also explains *imperatives* for people to share their data:

> We stress that patients must understand that it is their societal responsibility to make their anonymized data available to appropriate scientists and physicians so that the latter can create the predictive medicine of the future that will transform the health of their children and grandchildren (Bousquet et al. 2011).

In other words: Participation is a requirement for the holism of P4SM and the holistic medicalization it implies. It involves what Rose calls *a mode of subjectification*…

> …through which individuals are brought to work on themselves, under certain forms of authority, (…) by

> means of practices of the self, in the name of their own life or health, that of their family or some other collectivity, or indeed in the name of the life or health of the population as a whole (Rabinow and Rose 2006).

The participation of each patient consumer in novel social communities is a vivid example of what Rose's collaborator, anthropologist Paul Rabinow, terms *biosociality* (Rabinow and Rose 2006).

As a pioneering example of the wellness-regime that P4SM hopes to establish, computer scientist Larry Smarr has published results from 10 years of self-monitoring (Smarr 2012; Hood and Price 2014). Smarr employed multiple tools to measure his genome, blood markers (>100 variables), stool markers, diet, exercise, sleep and stress, pointing also towards more '*wholesome*' personal omics profiling in future *self-quantification*.

With reference to the *quantified self-movement* that Smarr pioneered (Table 1), we may predict that P4SM will contribute strongly to what Rose calls '*biological citizenship*' or '*somatic individuality*', the formation of a kind of personal identity in which '*we are increasingly coming to relate to ourselves as "somatic" individuals (…) who experience, articulate, judge, and act upon ourselves in part in the language of biomedicine*' (Rose 2007, p. 26). As an enabling factor of this development, some technologies (e.g. tracking devices) or at least their results (e.g. genome information) are becoming cheaply available to citizens. Technology is *democratized.* As a consequence, P4SM is presented as *democratizing* and *empowering,* enabling people to *know themselves* and establish *self-control* (Hood and Price 2014; Duffy 2015). However, to the extent that people will gain—or lose—genuine control of their life, they will do so according to the metrics of P4SM. To be in a position to define a metric of health according to which people manage their lives is power, an example of what Rose calls '*somatic expertise*' and *ethopolitics*, the latter meaning '*attempts to shape the conduct of human beings by acting upon their sentiments, beliefs, and values—in short by acting on their ethics*' through '*self-techniques by which human beings should judge and act upon themselves to make themselves better than they are*' (Rose 2007, p. 27).

We thus argue that what is most evidently '*democratized*' in participatory medicine is the ability to *self-medicalize*, and in P4SM more '*holistically*' than ever. Patients may become more active, but their goals are still defined by the agents behind P4SM. It should be noted that the leaders of the '*Hundred Person Wellness Project*' project (see Table 1) recently stated that most of its participants '*established a new and very personalized baseline for their own health*' through the research (Hood et al. 2015b). However, it is unclear at this point how each individual's personal baseline of health is thought established (e.g. is it defined using measures of subjective well-being or molecular markers?). It is also unclear how population-based metrics of health and each person's baseline are to relate (e.g. which one of them will actually define what health means in the individual case?).

Potential waste and harm

Control as value and goal

The extent to which health can in practice be given a meaningful scientific definition and controlled is an open question. However, one does not have to actually *succeed* in controlling human wholes for *holistic medicalization* to be realized. One only needs to *believe* it possible and make the attempt. As evident in the *quantified self*-movement, the values and goals of P4SM are likely to become defining to identities and actions in healthcare and beyond even before the framework is supported by empirical evidence (Lupton 2014; Wolf 2009; Smarr 2012). What are the values and goals of P4SM? Manifold, but we will state just one: *Control itself.* Physiologist Claude Bernard (1813–1878), who foresaw the application of mathematics to biology and has been called '*the first systems biologist*', can also serve as an historical reference for this ideal (Noble 2007). While Bernard had sophisticated ideas of living wholes, he also stated that '*When an experimenter succeeds in learning the necessary conditions' of the phenomena he is studying*, "*he is, in some sense, its master; he can predict its course and appearance, he can promote or prevent it at will*" (cited in Comfort 2012, p. 46). Consider also our opening quote by Loeb, who pioneered the biological engineering ideal so prevalent in P4SM. We see P4SM as biomedicine's latest and most all-encompassing step in pursuing this goal.

Beneficent and harmful medicalization

That said we want to stress that we see nothing inherently wrong with control or medicalization. Beneficent control is a key aim of medicine. However, as reflected in the ancient medical proverb '*first do no harm*', all medicalization also comes with caveats (i.e. '*overmedicalization*' or '*futile medicalization*'). A full discussion of all caveats implicated by the holistic medicalization of P4SM is beyond our scope, but we will point out what we find most fundamental.

False positives, overdiagnosis, opportunity cost

Firstly, the number of measurements and continuous (self)-management of well people will likely increase findings of uncertain significance, false positive tests, overdiagnosis and overtreatment (Diamandis 2015). Even if these problems were nullified, the sheer amount of work done by all involved agents would represent a significant *distraction* of attention and economic resources away from other problems and solutions that also matter in life (opportunity cost).

Social and cultural iatrogenesis

The most insidious danger, however, may be what Ivan Illich termed *social* and *cultural iatrogenesis* (Illich 1975): It may lead to a damaging labelling of aspects of life *as medical* and displace other valid goals, values and ways of understanding and tackling life. Biomedicalization may distort our understanding of problems that should be understood on the personal, social or political levels by describing them in reductive biological terms. The holism of humanistic medicine has traditionally considered health a phenomenon that is hard to separate from '*the good life*' itself (Hofmann 2002; Boenink 2009). When previous definitions of health have been deliberately 'vague', it is precisely because this phenomenon is exceedingly complex, an *enigma* defying any simple attempt at a definition (Gadamer 1996). In accounting for all its critical aspects, P4SM can never be truly *holistic* or *person-specific*. Like all science it must necessarily involve reduction and generalization (Vogt et al. 2014; Wolkenhauer 2014). If P4SM insists that it can eradicate the '*vagueness*' of health, it also risks denigrating the '*the good life*' by ignoring what its metrics cannot capture. As Downing states of '*biohealth*' (Downing 2011, p. 6).

> Health means wholeness; qualifying it by "bio-" narrows it down to a certain sort of wholeness, that which is brought about by the application of the biological sciences. Those applications may be very beneficial, but those benefits cannot be called health, because they are not whole.

Critically, while the holism of what we have called humanistic medicine has focused on what is *good enough* in life and exercised a certain tolerance towards disease, we cannot find the possibility of health being *compatible with disease* mentioned in our material. Even more profoundly, the fact that everyone eventually grows frail and dies—and how to handle this—is completely absent from P4SM as a proposed framework. As evident in one of its policy requirements, P4SM is instead associated with *perfectionism*: '*Set a benchmark for the U.S. to become the "healthiest nation", like putting a man on the moon*' (Hood and Galas 2008). Evidently, P4SM risks creating illness-generating and cost-increasing expectations of wellness (Callahan 1998).

Narratives versus bio-narratives

Our species is biologically defined by an ability to generate meaningful stories that define our lives and sense of health (Cassell 2013). What P4SM promises to do through its continual monitoring and modelling is to redefine such life stories as what we may call technoscientfically constituted *bio-narratives*. In a very real sense, it amounts to a new '*bio-narrative medicine*', promising literally '*to develop a series of stories about how actionable opportunities have changed the wellness of the participants*' (Hood et al. 2015b). Such *bio-narratives* may potentially help document the importance of personal experience and agency, but they may also displace other narratives. Consider remarks made by researchers of the '*Hundred Person Wellness Project*':

> Almost all individuals came to the study with the view that they were (for the most part) well. However, the study exposed for all individuals multiple actionable possibilities that could be acted upon to improve their wellness. This illustrated that most of us have unrealized potential for optimizing our wellness (Hood et al. 2015b).

These people entered the clinic feeling healthy, but according to their *bio-narrative*—as interpreted—they '*in fact, have multiple abnormalities in biochemical markers reflecting organ and system dysfunction, nutritional status or other health risk*' (Hood et al. 2015a). In this case, each participant's experience of health seems trumped by P4SM metrics. There is no scientific reason, however, why the *bio-narrative* should be privileged in defining health. This is, at least in part, a conceptual question.

The last well person

Hood and coworkers have argued that damaging effects from risk information and positive findings is '*a myth*' (Hood et al. 2015a). Rather than going into an empirical discussion about this disputable conclusion, we will make a philosophical argument that *holistic medicalization* must by necessity have major disruptive effects on human life. As philosopher Hans-Georg Gadamer puts it, '*health itself*' is the ability to '*forget that one is healthy*' (Gadamer 1996, p vii). This would seem impossible in P4SM. What is at stake is no less than a person's own ability to state '*I am well*' without having to consult a computational mirror image. In a 1994 article in The New England Journal of

Medicine, M.D. Clifton K. Meador satirically predicted the demise of what he called '*The Last Well Person*', noting that '*Well people are disappearing.* (…) *I began to realize what was happening only a year ago, at a dinner party. Everyone there had something*' (Meador 1994). If P4SM defines 100 % of the population with something '*actionable*', it is risks fulfilling Meador's prophecy.

Conclusion

We have argued that what we have called the technoscientific holism of P4SM points towards a '*holistic medicalization*', to date the most systemetic and comprehensive expression of a broader '*medicalization of health and life itself*' that may also define the limits of medicalization in the future. With P4SM the '*divide and conquer*' of previous reductionist biomedicine is replaced by '*synthesize and conquer*'. It moves from hoping to control disease by manipulating of a few factors to hoping to control it through management of the whole, dynamic life process. This is not a return to the holism of humanistic medicine, as in medicine that is focused on the defining capacities, subjective experience and values of whole persons. Rather, it is biopsychosocial, patient-centered and person-centered medicine—or the '*art*' of medicine—being redrawn in technoscientific terms.

Despite launching an unprecedented expansion of medicalization, P4SM advocates have not yet engaged in judicious discussions of potential downsides. We therefore want to conclude by affirming that its *holism* calls for *quaternary prevention*. Quaternary prevention is a growing thrust in preventive medicine aiming to '*Reduce overmedicalization (overdiagnosis and overtreatment) and iatrogenic harm*' through '*action taken to protect individuals (persons/patients) from medical interventions that are likely to cause more harm than good*' (Brodersen et al. 2014). The words of biologist Carl Woese (2004) calling for *a new biology for a new century* also seem relevant for health care and preventive measures in the coming years: '*A society that permits biology to become an engineering discipline, that allows that science to slip into the role of changing the living world without trying to understand it, is a danger to itself*'.

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Paper III

Personalizing Medicine: Disease Prevention *in silico* and *in socio*

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ABSTRACT

Proponents of the emerging field of P4 medicine (defined as personalized, predictive, preventive and participatory) argue that computational integration and analysis of patient-specific "big data" will revolutionize our health care systems, in particular primary care-based disease prevention. While many ambitions remain visionary, steps to personalize medicine are already taken via personalized genomics, mobile health technologies and pilot projects. An important aim of P4 medicine is to enable disease prevention among *healthy persons* through detection of risk factors. In this paper, we examine the current status of P4 medicine in light of historical and current challenges to predictive and preventive medicine, including overdiagnosis and overtreatment. Moreover, we ask whether it is likely that *in silico* integration of patient-specific data will be able to better deal such challenges and to turn risk predictions into disease-preventive actions in a wider social context. Given the lack of evidence that P4 medicine can tip the balance between benefits and harms in preventive medicine, we raise concerns about the current promotion of P4 medicine as a solution to the current challenges in public health.

keywords: personalized medicine; systems medicine; primary care; systems biology; p4 medicine; medicalization; big data; disease prevention; overdiagnosis.

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1. Introduction

An important goal of *in silico* medicine is to improve biomedical research through computational integration of big data. This paper examines the challenges of implementing systems medicine (the medical application of systems biology) in primary health care. Specifically, we focus on the ramifications of strategies aiming to improve disease prediction and prevention through *personalization* of medicine, a concept promoted as P4 medicine that is *predictive*, *preventive, personalized* and *participatory* (Alyass et al., 2015; Benson, 2016; Duffy, 2015).

The goal of personalized medicine is as old as the profession, and can broadly be defined as the aim to account for those factors that make health and disease specific for each individual. What is new about P4 medicine is its emphasis on doing so "*in silico*" via data-integration, and "*in socio*" via *patient participation* in data collection and disease prevention. P4 medicine is based on the expectation that "big data" technologies can account for an increasing number of factors that influence health and disease, and that these data can be used to stratify the population and health problems according to various characteristics. Big data here refers to patient-specific data from various sources such as genomics, "phenomics" technologies that enable monitoring and self-monitoring of phenotypic biomarkers, health records, as well as "exposomics" that provide inputs on environmental exposure (Flores et al., 2013; Gjuvsland et al., 2013; Wild, 2012). The hope is that *in silico* computational integration of these data will generate a more complete understanding of each person´s health, better risk predicting algorithms and effective preventive strategies. *In socio*, its implementation in the context of each socially embedded person´s life requires a change in the current structure of health care towards increasing patient participation in data collection, self-management and prevention of future diseases. Through these strategies proponents expect that P4 medicine will increase the quality of care and lower the escalating costs of health systems (Bousquet et al., 2011; Flores et al., 2013; Kirschner et al., 2013; Diaz et al., 2013).

So far, important discussions about personalized medicine have considered ethical and legal issues such as informed consent, disclosure dilemmas, personal identity, data security, as well as the current discrepancy between marketing and the utility of genomic risk profiling (Bartol, 2013; Reydon et al., 2012, Rehman-Sutter & Müller, ed., 2009; Forgò et al., 2010; Juengst et

al., 2012). Our scope is wider in examining P4 medicine in general, and in discussing the overall clinical utility of the new preventive strategies for improving public health systems.

While P4 medicine also aims to target established disease with higher precision, we will focus on its primary strategy – to keep people healthy through individually targeted *predictive* and *preventive medicine*:

> Systems medicine aims at predicting the course of a disease in a given patient and how far it can be altered by available therapies. (...) The fundamental principle of systems medicine should thus be the prediction of benefit–risk for a single subject, a group, or a population" (Boissel et al., 2015, p. 138).

While P4 medicine aims to target the course of established disease with higher precision, P4 medicine also involves a stronger focus on healthy people through a more expansive and life-long detection of early disease and risk-factors using more data – literally "billions of data points" (Bousquet 2011, p. 7). In other words, P4 medicine constitutes a new form of continual *screening process*, which is unprecedented in intensity and scope (Vogt et al., 2016, Diamandis, 2015). For the balance of benefits vs. waste and harm to turn out positive, this radical expansion seems to presuppose very significant gains in the overall utility of preventive medicine. In this paper we examine challenges involved in achieving such a meaningful balance. Particularly, we critically examine an assumption that is often taken for granted, namely that large scale computational integration and analysis of "big" health data will lead to a preventive medicine with a more adequate utility (i.e. balance of benefits vs. harms and costs) (Flores et al., 2013; Kirschner et al., 2013; Topol, 2012).

The authors of this article bring together practice-oriented philosophy of science (SG) and philosophically oriented general practice (HV)[1] in an analysis of the clinical utility and societal implications of P4 medicine. In the context of the current paper, *clinical utility* is related to the concept of "actionability" used by proponents of P4 medicine (Hood et al., 2012). Utility and actionability presuppose not only that the early detection of disease and risk assessments have a high clinical validity (accuracy), predictive and prognostic power, but that they can be coupled to actions that show clinical efficacy and

[1] General practice (or family medicine) is the medical specialty that focuses on the whole patient, as opposed to subsystem-focused specialties. It is part of primary care, and often the point of access and "gate-keeper" to care. General practice is where most medical disease prevention takes place.

effectiveness as well as an adequate balance of benefits and harms in a wider clinical and societal context (Burke, 2014).

Thus, successful implementation of P4 medicine not only depends on its ability to accurately predict disease (detect very early signs of disease or risk factors), but also on its ability to translate these predictions into meaningful disease-preventive actions. The latter aspect requires that the strategies can work in clinical practice and people´s socially embedded lives. Historically, social aspects were at the center of personalized medicine as it was initially tied to a humanistic movement focusing not only on bodily fragments, but the uniqueness, experience and agency of the whole person over time (Cassell, 2010; Tutton, 2014). But whereas personalized medicine historically emphasized the person´s social context and the doctor-patient relationship, P4 medicine rearticulates the same goal via quantitative *in silico* models. This raises important questions about whether factors concerning social and human biocomplexity are sufficiently accounted for in strategies laid out to reach the ambitious goals of P4 medicine.

It may be objected to our analysis that these ambitious goals should not be taken seriously at this point. P4 medicine mostly exists as a set of promises about the future, and the published claims about the future of medicine may be seen merely as rhetorical strategies driving the competition for research funding. Admittedly, the above promises of P4 medicine are made with varying degrees of boldness, and current views on their soundness differ (Diamandis, 2015; Joyner & Paneth, 2015). However, they are published in scientific contexts, and accordingly may generate expectations and actions that influence choices concerning prioritization, funding and implementation of medical research and health strategies. Accordingly, we believe that researchers have a scientific responsibility to calibrate their promises to what can actually be expected of their methods and the consequences their claims may have (Forssén et al., 2011). We thus find it crucial to critically examine the promises, and the available evidence that may justify them. In the current paper we combine an analysis of P4 medicine´s science visions with historical insights into the challenges of disease prediction and prevention. Particularly, we highlight lessons from personalized genomic medicine and material summarizing the concrete results from a dedicated P4 medicine pilot project, the Seattle Institute for Systems Biology´s 'Hundred Person Wellness Project' (Hood et al., 2015a).

We begin by relating the promises of P4 medicine to the historical and current challenges in preventive medicine, particularly by examining the problems of producing findings of unknown significance, overdiagnosis, and overtreatment (Section 2). By examining the current status and future plans for P4 medicine, we then ask whether it is likely that *in silico* medicine will be able to better deal with such challenges by computational integration of patient-specific data. Section 3 examines the challenges faced for disease prediction, whereas Section 4 analyzes the challenges of turning risk predictions into disease-preventive actions in a wider social context. We point to the lack of evidence that P4 medicine can deal with the described challenges and raise concerns about the current promotion of P4 medicine.

2. Challenges of Waste and Harm: P4 Medicine in Light of the History of Preventive Medicine

2.1. A 'tipping point' in preventive medicine

As a form of individual-centric preventive medicine, P4 medicine establishes itself as the latest chapter in a longer story starting with the establishment of hypertension as a treatable risk factor for cardiovascular disease in the 1960s (Welch 2011, chapter 1; Getz 2006; Hamilton et al., 1964).

Individualized disease prevention has been associated with continued promises and high expectations (Yach and Calitz, 2014). It has certainly had its merits, but its success must be understood as relative to the problems it tries to solve, the expansiveness of its measures, costs and harms. Generally, preventive medicine has been most successful in cases where there is a relatively simple and strong relationship between risk factors and disease, e.g. patients with an established organ disease diagnosis or well people at very high risk (4S Study Group, 1994; Welch et al., 2011, chapter 1; Hamilton et al., 1964). However, preventive medicine has turned to more challenging problems, notably prediction and prevention of complex, non-infectious disease in a population of predominantly asymptomatic people at lower risk of disease. Compared to people at high risk, this demands more of the test´s capacity to predict disease and raise the probability high enough for action to be justified. In such cases, a higher number of patients must generally be treated in order to change one outcome ("number needed to treat"). In this

endeavor, preventive medicine has met with consecutive realizations that these problems are harder to tackle than expected.

Responding to these realizations preventive medicine has made its predictive and preventive efforts more expansive and complex, taking an increasing number of bodily factors and aspects of life into account. Critically, disease concepts have been widened by lowering diagnostic thresholds for what is regarded as "disease", "early disease" or "at risk" for each of these factors, thereby redefining an increasing number of people as in need of medical attention. An expanding number of risk factors in terms of biomarkers have been defined (Skolbekken, 1995; Getz, 2006, Petursson et al., 2009a, 2009b). As a corollary, clinical efforts have also expanded with more intervention strategies based on more measurements, including examinations of asymptomatic people to detect early disease or risk states (screening). As a result the scientific and clinical endeavor itself has been complexified, with more data to integrate and interpret, requiring more comprehensive and complex strategies.

P4 medicine may thus be seen as the culmination of a series of increasingly expansive efforts to improve predictive and preventive strategies to deal with the complexity of human biology and clinical practice. Today, we will argue, its advent coincides with a historical "*tipping point*" in the overall balance of benefits vs. harms and costs in preventive medicine (Starfield et al., 2008). On the whole, the strategies involved, such as implementation of preventive clinical guidelines, general health checks, screening and lifestyle counselling, seem not to work as effectively as expected in practice (Fretheim, 2007; Hetlevik, 1999; Krogsbøll et al., 2014; Jørgensen et al., 2012, Look Ahead Research Group, 2013). The reasons for this may be multi-layered. As one element, doctors may not follow guidelines (Ashenden et al., 1997; Hetlevik et al., 2008; Austad et al., 2015; Boyd et al., 2005). Another key problem is non-compliance of patients, particularly lack of response to risk assessments with sustained lifestyle changes (see Section 4). More fundamental, however, are concerns about negative effects of preventive strategies.

As a consequence, the last 20 years have seen an increasing concern in mainstream medicine about the overall utility, i.e. the balance of benefits and harms, of preventive medicine´s expanding efforts (Fisher & Welch, 1999; Sackett, 2002; Heath, 2013; BMJ; JAMA Internal Medicine). The waste and harm involved may be both *indirect* in terms of opportunity costs, where personnel and resources are diverted away from other issues, and *direct* in

terms of unnecessary side-effects and costs of diagnostics and treatments (Fisher & Welch, 1999; Welch et al., 2011; Heath, 2013; Moynihan et al., 2012; Hofmann, 2014). Although negative consequences are often not registered in trials (Heleno et al., 2013), and results are contradictory, diagnostic labelling and preventive measures have been associated with harm, e.g. distress and reduced quality of life (see e.g. Jørgensen et al., 2015; Haynes et al. 1978; Brodersen & Siersma, 2013). To understand the basis for the discussion of waste and harm, the following section will introduce key concepts denoting the important challenges of preventive medicine relevant for P4 medicine.

2.2. Key concepts in discussions on waste and harm

One way to conceptualize the expansion of preventive medicine described in Section 2.1. is as *medicalization* (Maturo, 2012). We will here define medicalization as the process by which aspects of life are defined in medical terms and underlain medical control (Vogt et al., 2016). Importantly, this definition does not imply that medicalizing an aspect of life is inherently negative. A main aim of medicine is *beneficent control*. However, any attempt to establish medical control comes with caveats of waste and harm (i.e. *overmedicalization*).

Perhaps the most banal problem involved in medical testing is what we can call *findings of unknown significance*. Any clinician, having for example used a biomarker to screen a patient, knows the feeling of getting test results back not knowing what to make of them, especially in light of uncertainties about the test's predictive power, the individual´s complex situation and the potential benefits and harms of further testing and treatment. Another, but related problem is *false positives*, i.e. tests that turn out positive when the person in fact *does not* have the disease (or risk factor). The opposite is the case for *false negative* results.

Overdiagnosis has been claimed to be "the biggest problem posed by modern medicine" (Welch et al., 2011, conclusion). It is defined as situations where an actual disease or risk factor is diagnosed in people who are mostly well, and where this condition will not actually come to influence future health, either because it disappears spontaneously without medical attention or remains asymptomatic until death from other causes. Overdiagnosis is hard to measure; it is not possible to know at the time of diagnosis exactly who will

suffer, but in theory those overdiagnosed can only be harmed (Brodersen et al., 2014, Hofmann, 2014). Overdiagnosis may also refer more generally to overmedicalization and processes leading to reclassification of asymptomatic or low risk individuals as in need of medical attention and subsequent overtreatment with a questionable balance of benefits and harms (Moynihan et al., 2012).

Whereas the optimism for improved health benefits of population screening was high in the 1990s and 2000s, recent meta-analyses show that intensified screening is strongly associated with higher rates of overdiagnosis and overtreatment (Moynihan et al., 2012). The difficulties of identifying the cases where risk factors or early signs of disease will pose future health problems is particularly telling if we consider screening programs for cancer. Despite strong associations between genetic risk factors and breast cancer, and despite 30 years of experience and development of advanced methods for early detection (mammography), the rate of overdiagnosis of breast cancer has turned out to be high (Løberg et al., 2015). It is estimated that 30%, or approximately 1,3 million women, diagnosed with breast cancer have been overdiagnosed because the tumors would not have developed into health problems (Jørgensen & Gøtzsche 2009; Bleyer & Welch, 2012). This raises important questions about the utility of population screening programs (Biller-Andorno & Diamandis 2015; Gøtzsche 2015; Biller-Andorno & Jüni, 2014; Gøtzsche & Jørgensen, 2013; see however Puliti et al., 2012 for a more positive view). Strikingly, the mortality rates not only for breast cancer but also for thyroid cancer, melanoma, kidney cancer, and prostate cancer have remained largely unchanged from 1975-2005, despite increasing rates of new diagnoses and treatment (Moynihan et al., 2012).

On a more general level, one key cause of waste and harm may be *fragmentation*. An editorial in the Annals of Family Medicine states:

> Underlying the current healthcare failings is a critical underappreciated problem: fragmentation – focusing and acting on the parts without adequately appreciating their relation to the evolving whole. This unbalance, this brokenness, is at the root of the more obvious healthcare crises of unsustainable cost increases, poor quality, and inequality. Fragmentation is at the heart of the ineffectiveness of our increasingly frantic efforts to nurture improvement" (Stange 2009, p. 100).

Human health problems have been categorized according to more minute bodily parts, and each factor is treated in separate "silos" of medicine (Parekh

& Barton, 2010). The sum of these parts, each with their diagnostics and treatments, adds up to "too much medicine", which may be wasteful, harmful and unmanageable in practice (Getz et al., 2005; Petursson, 2009b; Hetlevik et al., 2008).

One answer to the above challenges in preventive medicine is that science is simply not good enough in tackling the complexities and fragmentation involved, and that the solution lies in technoscientific breakthroughs. This is the position of P4 medicine (Vandamme et al., 2013). As proponents of P4 medicine also point out, current evidence-based prevention strategies are based on studies of large populations and therefore fail to capture patient-specific variation, thus potentially leading to poorer predictions and interventions, waste and harm (Topol, 2012).

However, what is at the same time often named as the foremost driver of increased medical costs and harm – notably also when it *does* have beneficial effects – is novel technology that enables more sensitive detection of disease and medical risk as well as attempts to improve prognosis (Bodenheimer, 2005; Callahan, 2008; Dybczak & Przywara, 2010; Moynihan et al., 2012; Hofmann, 2015). Yet, a solution based on more technology is precisely the promise of P4 medicine. This highlights the question whether P4 medicine can achieve a useful balance between benefits and harms.

3. The Utility of P4 Medicine: Disease Prediction in Clinical Practice

Based on the above discussion on the balance of waste and harm in screening and preventive medicine, we will now divide our further discussion of P4 medicine in three: In 3.1, we will discuss P4 medicine in light of lessons from *personalized genomics*, its immediate predecessor in preventive medicine. In Section 3.2, we will discuss early results from the first project that aims to pioneer *in silico* systems medicine. In 3.3, we look to the future and ask if we can expect more data and systems medicine to overcome tip the balance of utility in preventive medicine favorably. Our focus will mainly be on the diagnostic side and challenges of disease prediction, and less on the development of treatments for complex disease. However, we must underscore that this is an equally crucial step worthy of a publication of its own. If the prediction has no associated effective treatment, it is not actionable.

3.1. Genomic strategies and personalized genomics

The completion of the Human Genome Project was an important step in the development of biomedical, personalized medicine. Since the completion of the first human genome in 2003, the time and costs of sequencing of a human genome has decreased exponentially, enabling personalized genomics for large population groups. At the moment of writing, initial steps towards the development of personalized medicine are taken through the investment in large-scale projects such as the "Precision medicine initiative" (US) and the "100,000 genomes" (UK) project (Collins & Varmus, 2015; Marx, 2015). In addition to detailed whole genome sequencing, a prominent form of research underlying efforts in personalized genomics is genome-wide association studies (GWAS). The basic procedure of GWAS is to scan for genetic variants that are statistically significant when comparing two groups, typically a group with and without a specific disease. Risk alleles, or single nucleotide polymorphisms (SNPs), are said to be associated with a specific disease if its appearance among a group with a given disease is statistically significant compared to a group without the disease. GWAS have the dual aim of identifying new disease-related genetic variants for research purposes and to use the statistical estimates of disease risk for individualized disease prevention.

However, such GWAS-based efforts have already run into challenges of biocomplexity and prediction. To understand this we need a small historical detour. GWAS studies were originally designed to test the "common disease–common variant hypothesis", i.e., that common genetic variants could explain a large proportion of the variation in common diseases (McPherson & Tybjaerg-Hansen, 2016). Significantly, biologists warned from the beginning that:

> The common disease/common variant model is elegant, appealing and politically correct, but there are objections. The essential one is that it fundamentally misrepresents the nature of common disease. By definition, complex traits have (...) a low probability of carrying any particular susceptibility genotype given that the individual has a particular disease or trait phenotype. This is because, unlike Mendelian disorders, common diseases clearly result from the interaction of many genetic and environmental influences, so that the correlation with any one factor is weak" (Wright and Hastie 2001, p. 2).

The problem is here that each genetic biomarker has only a weak or modest association with a complex disease or *incomplete penetrance*.[2] In other words, a very large number of genes, each with small and context-dependent effects, are involved in determining disease and the exact causal relationship is complex and unknown (McPherson & Tybjaerg-Hansen, 2016). Researchers have major difficulties accounting for the heritability in terms of specific genetic variants even in cases where the heritability of a disease is high (Maher, 2008). This has created discussions about explanations for the "missing heritability". Some have suggested that the total heritability may be significantly inflated by gene-gene and gene-environment interactions, creating "phantom heritability" (Zuk et al., 2012). The importance of dynamic interactions means that the causal influence of any particular genetic risk factor is not stable and additive, but dependent on the biological and environmental context. This has discouraging implications of the predictive potential of gene tests (Wallace, 2012). While it was previously hoped that one could find variants that multiplied the risk 600%, the detection of variants rarely increase the probability of disease by more than 50% (Joyner &Paneth 2015; Kaiser 2012). This decreases the utility of such findings. While 50% may sound substantial, remember that when the probability of any given disease is initially low, which is often the case in well individuals, the test needs to raise the probability of disease substantially to add something useful to clinical judgement.

The aforementioned issues do not reject the potential for genomic strategies to play important roles as correlation-based research heuristics to identify candidate gene variants for further causal analysis. However, important concerns are raised in cases where SNP analyses are used as what Austin and colleagues (2013) call "shot-gun testing", i.e., simultaneous screening for multiple risk factors (e.g. in consumer genomics today). The (often unknown) causal complexity and incomplete penetrance between genetic variants and disease increases the challenges outlined in section Section 2, as we clarify below.

[2] Penetrance of a mutation is a statistical measure for the phenotypic impact of a genetic variant.

3.1.1. Personalized genomics: Variants of unknown significance

With new genomic strategies, the problem of findings of unknown significance has greatly increased in terms of so-called *variants of unknown significance (VUS)*. As one commentator working within genetics puts it, genome data today are "routinely failing to reveal useful insights about disease in general or a person's health in particular" (Cooper, 2015, p. 1423). In many cases, information about genetic associations is no more predictive of disease risk than factors such as family history, environmental risk, age, blood pressure etc. (Hall et al., 2010; Joyner &Paneth 2015). According to Cooper, "Such variants are trapped in the interpretive void between "benign" (i.e., definitively not relevant to disease) and "pathogenic" (i.e., definitively relevant to disease)" (Cooper 2015, p. 1423). What is deemed *significant* is also not only objective, but a culturally situated and value-laden act of interpretation: "Your VUS may be my diagnosis, depending on the manner in which we use the information and the weights that we place on the consequences of false positive and false negative conclusions" (Ibid., p. 1424).

3.1.2. Personalized genomics: False positives and false negatives

Uncertainties associated with genetic markers, the cumulative effects of these, and sampling procedures for GWA approaches also increase the problem of false positives and negatives (Ng et al., 2009; Tutton, 2014). On the basis of the expected high numbers of such results, critics of consumer genomics have stressed concerns about increased and unnecessary anxiety about future diseases and risk information, or a false sense of "genetic immunity" from these (e.g., Ransohoff & Khoury, 2010). Such concerns have not been sufficiently supported by empirical studies of self-reported reactions from early users of consumer genomics (Nordgren, 2014; O'Daniel et al., 2010). However, it can be questioned whether early users are representative of the general public, as admitted by the authors of one of these studies (MacGowan et al., 2010). This point is particularly important at the background of other studies documenting psychological distress associated with false positive results in the context of risk profiling for breast cancer (Brodersen & Siersma, 2013).

3.1.3. Personalized genomics: Overdiagnosis

The cancer researcher Gilbert Welch has stated that genetic testing should be considered the ultimate form of overdiagnosis, as virtually everyone will be diagnosed with risk factors (Welch et al., 2011). Many genotypes are weak predictors and, "Overdiagnosis and penetrance are inversely related. The less penetrant a gene is, the more overdiagnosis will occur, because most people with low-penetrance genes will not in fact go on to develop the disease" (Welch et al., 2011, chapter 9).

Generally, the benefits and harms of predictive and preventive interventions are not only influenced by the sensitivity of the testing procedures, i.e. their ability to detect disease, but also by factors associated with the absolute risk of a certain group. For instance, screening for different types of cancer is typically recommended only for particular age groups or for people with a higher expected risk due to their family history. Of particular relevance for further investigation is therefore whether personalized genomics can help identify the individuals for which further screening and monitoring is advisable. If so, personalized genomics could help health care providers tailor screening programs only to individuals that are most likely to benefit from these. Yet, we must in this context keep in mind the levels of uncertainty for shotgun tests for risk factors with low penetrance, compared to more traditional genetic tests for BRCA mutations and the concerns mentioned in Section 2 about overdiagnosis in screening programs.

3.2. Early evidence of P4 systems medicine in practice

With GWAS and personalized genomics, P4 medicine started out as a gene-centric project, focusing mostly on DNA. However, P4 medicine has increasingly seen the need to account for biological systems *as wholes*, whether in terms of whole pathways, whole cells, whole organs or even the whole human organism as *a system of systems* (Bjørnson et al., 2016; Flores et al.; 2013; Diaz et al., 2013). It is this development that is called *systems medicine*. So far, attempts to increase the predictive power of testing by using algorithms that combine several variables (e.g. smoking, cholesterol, blood pressure) have lead to misclassification and overclassification of risk status (Getz et al., 2005; Petursson et al., 2009b, 2012; Kolata 2010; van Staa et al., 2013). Although some significant progress has been made (Mega et al., 2015), the addition of

genetic information to such algorithms has generally also had limited success (McPherson & Tybjaerg-Hansen, 2016; Smith et al., 2015). This has strong relevance for P4 medicine, which acknowledges the weaknesses of previous tests, but promises to overcome the complexity involved by increasing the number of variables dramatically. As a tell-tale development, cardiovascular disease prevention, which started out 50 years ago with hypertension as a single biomarker, is now moving towards the use of high-throughput methodology and systems biology to improve prediction and prevention (McPherson & Tybjaerg-Hansen, 2016; Bjørnson et al., 2016). Thus, both the data and proposed algorithms involved in systems medicine are becoming even more complex. As preventive medicine stands at the tipping point described in Section 2, and the journal *JAMA Internal Medicine* (see reference list) as one example highlights "*less is more*", P4 medicine proposes to tip the balance of benefits and harm through *even more* medicine.

A project that may be seen as defining for the current status of P4 medicine is the Hundred Person Wellness Project (HPWP), performed in 2014 by the Institute for Systems Biology (ISB) in Seattle and prominently featured in *Nature* (Gibbs, 2014). This pilot study is important for our purposes, as it is the first real-world test of P4 medicine as conceptualized by the key visionary, biologist Leroy Hood.

The HPWP pioneers the most radical medicalization of human life in history. In total, 107 participants, mostly Caucasian, middle class and predominantly asymptomatic persons were included, each constituting a form of n-of-1 research project over 10 months. They were underlain a regime of fine-grained, multi-level and longitudinal monitoring aimed at the earliest possible detection of disease and risk factors, that is, a continual *screening process* of unprecedented scope. According to Hood et al. (2015a), patient-specific data were collected in "four main areas: 1) whole genome sequencing; 2) clinical and functional laboratory testing (every three months); 3) gut microbiome (every three months); and 4) quantified self and traits (physical activity, sleep, weight, blood pressure, personality and lifestyle factors, and so on)". These data were used as a basis for advice from health coaches (a novel primary care professional). In addition, a variety of proteomic and metabolomic markers were measured, creating individualized clouds of billions of data points for each individual to be computationally integrated and mined. The researchers aim to expand the HPWP to 100,000 participants in a "100 K Wellness project".

Little empirical evidence has been published about the clinical utility of P4 medicine or the HPWP. Recently, however, some early results from the HPWP and cases that are used as "proof of principle" narratives have been described. In our below discussion of these reports, the concept of actionability and "an actionable", which is frequently used by Hood and coworkers will be central. Hood & Price (2014, p. 22) have vaguely defined "an actionable possibility" as "a feature for an individual that, if corrected, could improve wellness or avoid disease".

3.2.1. Actionable gene variants: The case of vitamin D

Personalized genomics forms an integral basis of the HPWP and P4 medicine, and we will first examine this element in light of Sections 2 and 3.1. In their promotion, Hood and colleagues refer specifically to the concept of an "actionable gene variant", defined as a defective gene "that allows a physician to specify how a patient may improve his or her health" (Hood et al., 2012, p. 5). Furthermore, they claim that, "It is the continually increasing number of actionable gene variants that will be the major driver in having society accept whole genome sequences as an important part of each person's medical record" (Ibid, p. 5). Hood (2013, p. 9) claims that, "All individuals will benefit from sequencing their genome" due to the identification of such variants, and furthermore that "We have identified almost 300 highly penetrant variants that fall into the actionable gene variants category". Many of these "actionables" are supposedly linked to nutritional deficiencies (Hood & Price, 2014). In light of sections 2 and 3.1, this seems a high number, and we may ask: Why should these variants be regarded as "actionable"?

Hood and colleagues have in various publications exemplified what they mean by an "actionable gene variant" by describing the case of a man that is diagnosed with a gene that codes for a malfunctioning vitamin D transporter protein (Hood et al., 2012; Hood, 2013; Hood & Price, 2014). This variant is described as potentially leading to osteoporosis with early onset. The man is then described as being able to reverse this condition and prevent it from reoccurring by taking over time x20 the normal dose of vitamin D (or calcium according to Hood & Price, 2014).

Should this genetic variant actually be considered "actionable" in the sense Hood and colleagues define it above, and what does this mean for the status of the other 300 variants referred to? As Hood and colleagues do not refer to

clinical or other research on the 300 variants or the vitamin D case, which (as far as we can see) has not been described in a separate publication, this is unclear. However, from what is recounted the treatment in the case seems to be based solely on physiological reasoning about disease mechanisms. In general, this kind of reasoning has a problematic track record in medical decision-making (e.g., Echt et al., 1991). Additionally, Hood and colleagues do not mention eventual side effects of the x20 dose of calcium/vitamin-D. Taking vitamins (or calcium) may sound innocent, but side effects should always be taken into account. However, our main point here is that as an example of how "actionability" or "clinical utility" should be understood in P4 medicine, this case fails to give a clear and persuasive account.

3.2.2. Results and utility of the HPWP

Three publications and one plenary speech provide some preliminary results from the HPWP (Hood et al., 2015a; 2015b; Schmidt, 2014; Hood 2014):

- The project diagnosed "multiple 'actionable possibilities' for each participant" (Hood et al., 2015b).
- 57% were diagnosed with an actionable "cardiovascular pattern" (abnormal lipids, particle size or density), 53% with an "inflammation pattern" (elevated inflammatory markers) and 63% were diagnosed with an actionable "nutrient insufficient pattern" (defined as "decreased levels of key nutrients") (Hood, 2014). Regarding nutrition, the measurements had especially revealed vitamin D deficiency (Schmidt, 2014). Recommended actions against these "actionables" ranged from medication and supplements to dietary change, exercise, weight loss and stress management (Hood, 2014).
- 43 participants were diagnosed with *prediabetes*. 7 individuals were reported to have normalized and "many others had favorable improvements" in their prediabetes markers by the end of the study (Hood et al., 2015b).

Previous studies in Norway have shown that if one follows authoritative guidelines for disease prevention in a normal population, one would define a high proportion as "at risk" (Getz et al., 2005; Peturson, 2009). What is most striking about the above described results is that – at least as pioneered in the HPWP – the P4 medicine preventive strategy seems to define 100% of a

population of previously well as in need of medical attention. It is also striking that over half the population is diagnosed with a risk factor both with regard to CVD, nutritional status and inflammation. Of relevance, vitamin D deficiency and supplementation in asymptomatic people is a highly controversial issue in current debates on waste and harm, which is linked to poor clinical evidence as well as alternative medical practice (Welsh & Sattar, 2014). Also of relevance, prediabetes, an extension of the diabetes category with a lower diagnostic threshold, is a controversial case in ongoing debates on overdiagnosis as it may entail the downsides of being diagnosed with diabetes (costs and risk of treatment, challenges with insurance and employment, self-image) alongside questionable long-term benefit (Yudkin & Montori, 2012).

The above firstly raises important conceptual questions. Critically, it raises questions as to how the diagnostic thresholds have been defined. An "actionable" seems to be a rebranding of a finding that predicts disease, risk or at least something *suboptimal*. However, from the P4 medicine literature, there is conceptual unclarity as to what an "actionable gene variant" or "an actionable possibility" actually should correspond to in terms of utility and balance of benefits and harms. One may for example ask if detection of "actionables" points towards something more or different from what can be gathered from general, traditional health advice. Therefore, more conceptual work on what constitutes actionability and clinical utility in P4 medicine is needed.

Secondly, and most importantly, it raises questions about clinical utility. According to its lead scientists, many participants of the HPWP realized that with the information they could make decisions to improve their health and that "this can have enormous effects on reducing risk for downstream debilitating and expensive chronic and other diseases. This is central to reducing the cost of healthcare" (Hood et al., 2015b, p. 12). Without further documentation, Hood and colleagues insist that the benefits of their approach will "far outweigh any possible harms" (Hood et al., 2015a, p. 3). However, in light of our previous discussion on the history of preventive medicine, preventive genomics included and the enormous amounts of measurements and intensive management in previously well people in the HPWP, this is far from clear. The burden of proof should be regarded as heavy and entirely on the side of P4 medicine researchers.

Consider also *the law of diminishing returns*, which has been referred to since the beginning of discussions of waste and harm in mainstream medicine (Fisher & Welch, 1999). First described by economists this refers to the general trend that the first unit of input into a system (e.g. a unit of health care) will provide substantial benefit. However, for additional units (e.g. tests and treatments) the benefit decreases, and eventually, as each additional unit can offer comparatively little to previous units, the benefits of "more medicine" are eventually outweighed by the harms and costs.

At the time of writing, it is uncertain how much "actionable findings" add to current estimates of disease risk (or suboptimal health) in the individual. It is also unclear to what extent they can be coupled to interventions that have documented efficacy and effectiveness and can be predicted to change the prognosis in a real-life setting. The extent to which the massive number of "actionables" actually should be regarded as findings of unknown significance or overdiagnosis is thus unclear, but both must be regarded as potentially substantial. Screening for *risk factors* and an extreme focus on early detection of and intervention towards disease in asymptomatic people, as well as widening definitions of what is "actionable", increases the probability of overdiagnosis (Diamandis, 2015; Moynihan et al., 2012). The researchers themselves do acknowledge that, "It is inevitable that screening thousands of data points will generate false positives, as well as false negatives" (Hood et al., 2015a, p. 2).

More empirical evidence is thus needed to make a qualified evaluation of the HPWP. However, despite available guidelines for the assessment of evidence for and against the public health impact of personalized genomics, pilot studies such as the HPWP do not follow such guidelines, nor do they involve controls in order to evaluate interventions (cf., Diamandis, 2015; Hood et al., 2015a; Khoury et al., 2012).[3] Instead, the HPWP has a form of "*n-of-1*" research strategy of each individual that aims "to develop a series of stories about how actionable opportunities have changed the wellness of the participants – or made them aware of how they can avoid disease in the future" (Hood et al., 2015b). Although we will not dismiss such data-rich "bio-narratives" as informative, this makes it difficult to critically evaluate the results, and P4 medicine risks justifying the massive medicalization with

[3]For a reexamination of the Wilson-Jungner criteria for screening in the context of genomics and personalized medicine, see (Andermann et al., 2008; Diamandis, 2015).

anecdotal evidence. Additionally, the endpoints used in the HPWP seem mostly to be surrogate markers (e.g. blood sugar). However, continual correction of such markers is no guarantee that one can change the hard endpoints that actually matter (morbidity and mortality). Unless documentation is provided of what was actually done and achieved in the HPWP, the high profile project cannot be regarded as a credible scientific endeavor. Given its high profile in the promotion and promises of P4 medicine this is disconcerting.

3.3. Is more "big data" the solution for predictive and preventive medicine?

Having recounted the story of predictive and preventive medicine so far, including the HPWP, we now turn to its envisioned future. As mentioned in Section 2, what is exciting about P4 systems medicine is its promise to overcome fragmentation and "to provide the tools to take into account the complexity of the human body and disease in the everyday medical practice" (Vandamme, 2013, p.1-2; see also Mayer-Schönberger & Cukier, 2013). Ironically, however, what initially happens in P4 medicine is the most massive *fragmentation* in medical history through the gathering of fragmented big data.

The hope is that one can deal with multi-causality and overcome low predictability of complex diseases by accounting for an increasing number of risk factors. At least when considering the early results of the HPWP, each fragmented abnormal measurement seems to be taken as "an actionable", and when *interactions* between elements are taken into account, this is promised only to yield even more actionables (Hood et al. 2015b, p. 13). Risk profiling based on self-monitoring or gene testing results in an explosion of data points and factors of uncertainty – a challenge that physicians are not prepared for (Haga et al., 2012; Stanek et al., 2012). As Jameson and Longo (2015, p. 4) ask, "How can physicians adapt to this daunting explosion of information and the associated clinical guidelines?" The concern is that the sum of the fragmented measurements in P4 medicine adds up to an unmanageable amount of isolated diagnoses, treatments and considerations, each with a risk of waste and harm. A central premise for P4 medicine to work in practice thus seems to be that the vast amount of fragmented measurements can be *integrated* into models and algorithms so that *more* measurements can be translated into *less* waste and harm by registering only what is actually significant.

Proponents of P4 medicine expect that complex models can not only overcome many of the problems with traditional models, resulting from priorities on what to measure (cf., Kolodkin & Westerhoff, 2011), but also help identify the relevant variables as measures of health states and *stratify* the patient groups in need of particular treatments or health-optimizing actions (Hood and Flores, 2013). However, it should be noted that it is not always the case that more data will lead to better predictive models, while it is always the case that it comes with the caveats described in Section 2. Whereas the initial expectation that access to omics data would uncover underlying disease mechanisms via more complex models were high, it is becoming increasingly clear that there are serious practical and principal limitations to the idea of bridging the gap between genotypes and phenotypes via more datapoints (Noble, 2012; Wolkenhauer & Green, 2013). As proponents of systems medicine themselves admit: ″There is an urgent need to bridge the gap between advances in high-throughput technologies and our ability to manage, integrate, analyze, and interpret omics data″ (Alyass et al., 2015). One challenge is that the amount of noise inherent in the data increases as big data are collected, and handling and integrating large amounts of data pose a number of substantial challenges (Benson, 2016). These challenges include uncertainties about and differences among experimental methods and sampling procedures for statistical correlation studies, making data curation a much more complex matter than often assumed (cf. Mayer-Schönberger & Cukier, 2013; Leonelli, 2014).

Moreover, the hope of predicting and preemptively controlling disease raises fundamental questions about the general predictability and controllability of extremely complex systems (Cilliers, 2013). Such discussions are beyond the scope of this paper, but we wish to point to some lessons of systems thinking, and in particular challenges posed by the complexity of human biology and health, which is adapted to a complex social environment.

George Engel, founder of the widely recognized biopsychosocial medical model, formulated the challenge facing "personalized medicine" as the challenge of being *scientific in the human domain* (Engel, 1997). "*The human domain*" is here to be understood as *human biology* in the widest sense, as a complex, dynamic system. Health and disease emerges from an interaction between the biological, psychological and the social levels. As a modern recognition of these insights, scientists are now pointing out that a gene-

centric focus "will stymie progress" (Wild 2010, p. 1). For this reason, proponents of P4 medicine want to extend measurements to include "phenomics" (Gjuvsland, 2013) and "exposomics", the latter of which seeks to represent "every exposure to which an individual is subjected from conception to death" including the socioeconomic and "psychosocial" (Wild, 2010). But what are the reasons to believe that this will solve the problems involved in disease prediction and prevention?

Serious challenges are met in cases where there are complex feedback relations between molecular and social factors and adaptation to extremely complex social interactions. An increasingly rich biological literature from fields such as psychoneuroimmunology, epigenetics, psychosocial genomics and epidemiology documents how social and personal (psychological) experience of each individual affects the cellular and molecular levels (Marmot, 2005; Shonkoff et al., 2009; Holt-Lunstad et al., 2010; Danese & McEwen 2010; Eisenberger & Cole, 2012). Consider, as a striking example, how it is documented how neural circuits – notably the vagal nerve – relay signals from the socially situated brain to modulate the function of immune cells (Pavlov & Tracey, 2015). Such results empirically substantiate how the conceptual divides between nature and nurture, and mind and body, are untenable (Kendler 2005; Beauregard, 2007; Novack et al., 2007; Noble, 2012).

Our aim is not to reject that progress can be made, but to point out that the promises of P4 modeling strategies depends on the extent to which human biology, including the aspects we call "mental" or "psychosocial", are predictable and controllable at all (Strand et al., 2004; Vogt et a. 2014). Already in his book, *The Mirage of Health* from 1959, biologist René Dubos forcefully argued that, "exact science cannot encompass all the human factors involved in health and in disease" (p. 219). P4 medicine (still) cannot parameterize and measure this totality. Mapping the human genome has not changed the view that: "The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms' (Sulston & Ferry, 2002, quoted in Noble, 2010). So far at least, we have no reason to assume that one can "measure everything" to faithfully or meaningfully capture the factors that influence human health and disease, with unknown, but potentially very significant consequences for disease prediction and prevention.

We do not deny that *some* or perhaps *many* significant predictions with time can be made via the P4 approach. Particularly, the clinical utility of genome sequencing is a moving target that may greatly increase with the development of reference-genomes made from deep sequencing of large populations. Our main issue is again with the discrepancy between the promises made on the hand, and the lack of evidence and theoretical justification that P4 strategies can deal with the complexity on the other. This has profound implications for the prospects of P4 medicine to improve public health practices.

4. "Participatory": Challenges and Implications of P4 Medicine in socio

In Sections 2 and 3 we have outlined some scientific challenges to predicting and preventing disease in complex human organisms through "personalized" *in silico* strategies. In this section, we widen our critique and the meaning of "human biocomplexity" by examining challenges and implications related to its implementation in a social context. Advocates of P4 medicine acknowledge that, "This societal challenge of deploying P4 healthcare is more daunting than the scientific and technological challenges facing P4 medicine" (Flores et al., 2013, p. 5). However, they mainly point to conservative viewpoints and methodologies of the medical establishment, regulation issues and reimbursement policies favoring "disease care" over prevention (Topol, 2012, Flores et al., 2013). Our focus will be on a different, and arguably more fundamental, challenge associated with the presupposed reactions to risk information. The issue concerns the extent to which the norms and goals of P4 medicine and the reality of patients are aligned.

4.1. Will P4 risk information be "actionable" for the general public?

Would P4 medicine be effective and useful, even if it had valid predictions and efficient treatments? An affirmative answer presupposes that individuals react to risk information by taking action to improve health outcomes via lifestyle changes or preventive treatments. Proponents of P4 medicine seem to assume that risk information consists of value-free facts that are directly translatable into risk-reducing actions. Moreover, they assume that the goals inherent in P4 medicine are perfectly aligned with other goals in personal life and society (e.g. Hood et al., 2012; Hood and Price, 2014).

A view from social science reveals that response to risk information is a much more complex issue (Lupton, 2012; Prainsack, 2014). As noted in Section 2, evidence from the history of preventive medicine suggests that so-called "compliance" issues are still immense hurdles for preventive strategies. Proponents of P4 medicine respond to such concerns by arguing that P4 medicine will provide a whole new level of motivation compared to previous population-based healthcare. It is argued that individualized risk information will be perceived as more relevant, and that the immediate feedback provided by continual testing, primary care-based health coaching and social networking between participants will create "relationship-based accountability" (Hood et al., 2015a, p. 4; Hood et al., 2015a, p. 11). Yet, empirical studies show little or no effect of risk information from personal genetic risk profiling, in particular on health-related actions (Hall et al., 2010; Heshka et al., 2008; Marteau et al., 2010; Nordgreen, 2012; Roberts & Ostergren, 2013, Grant, 2013). Moreover, a recent randomized controlled trial, which provided participants with common, chronic health conditions with an extensive self-monitoring system and follow-up over 6 months, showed no short-term effects on health care utilization or costs (Bloss et al., 2016).

In some cases, concerning serious hereditary diseases, attempted risk-reducing behavior is documented in response to individual genetic risk profiling and thereby taken as a "proof of principle" of the benefits of P4 medicine. For instance, a study of responses among women with a high risk of breast cancer considers prophylactic surgeries, screening, and encouragement to further testing of close relatives ″a model for high-risk actionable genetic tests of proven clinical utility" that provide "clear benefits to participants″ (Francke et al., 2013, p. 1; see also O'Daniel et al., 2010). However, as we emphasized in Sections 2 and 3, it cannot be assumed without further evidence that the genetic tests identify the persons for which further screening is advisable, or that more screening of asymptomatic individuals will result in health benefits and reduced medical costs (Hall et al., 2010; Biller-Andorno & Diamandis 2015; Gøtzsche 2015; Biller-Andorno & Jüni, 2014; Gøtzsche & Jørgensen, 2013). Furthermore, an important driver of cost escalation in health care is the introduction of medical technology itself, previously estimated by health care economists to be as high as 40-50% of the annual cost increases (Callahan, 2008).

These points are particularly relevant for the evaluation of the HPWP project. Its leading scientists recently claimed that their early results are proof of principle that actions of their participants are changing this picture since "most of them established a new and very personalized baseline for their own health and 70% of them acted on the coaching recommendations provided" (Hood et al., 2015b). However, as it is also the case for early users of consumer genomics, it seems highly unlikely that the selection of a population of largely middle class "health enthusiasts", a number of whom reportedly felt that pioneering the P4 project was " the experience of a lifetime" (Hood et al.., 2015b), is representative of the general population or those at highest risk. From a public health perspective, Burke and Trinidad (2011, p. 1) stress that "P4 medicine cannot solve the root problem: the need for political and public health action to improve the life chances of disadvantaged people. In this context, a realistic assessment of the prospects for systems biology is sorely needed". A related concern is the potential harmful effects of risk information (e.g. stress and anxiety), particularly when the information most likely involves high rates of false positives and overdiagnoses (e.g. Diamandis, 2015). P4 proponents have dismissed such concerns as a myth with reference to studies of early users of consumer genomics and highlight that health coaching is accompanied by information of uncertainties about test results (Hood et al., 2015a). But, again, evidence of negative psychological effects of false positives in population screening programs (e.g., Brodersen & Siersma, 2013) cannot be dismissed with reference to studies of health or technology enthusiasts that are not representative of the general public. Moreover, the implementation of testing programs with a doubtful or unknown balance between benefits and harms cannot be justified with reference to informed choice (Johansson & Brodersen, 2015). That is, information about uncertainties does not remove the burden of evidence for the benefits of the tests from companies, scientists or health authorities.

The idea that choices about testing can be left to individual patients is particularly concerning given that the majority of the general public seems to overestimate the benefits of screening (Gigerenzer, 2009). The cultural perception of screening is difficult to change, even if patients are given concise information about the risk of overdiagnosis (Henriksen et al., 2015). The cultural belief that more medicine is better, and the widespread faith in early detection and screening is currently considered some of the main drivers of overdiagnosis (Moynihan et al., 2012, Heath 2013, Hofmann 2014).

Moreover, a key driver of overdiagnosis is technology itself. The technologies of P4 medicine aim to detect ever smaller "abnormalities", thereby widening the scope of medicine through a re-articulation of healthy people into "risk individuals". The researchers involved in the HPWP reported that "Many individuals who report that they feel reasonable 'well', may, in fact, have multiple abnormalities in biochemical markers reflecting organ and system dysfunction, nutritional status or other health risk" (Hood et al, 2015a, p. 2, see also Hood et al., 2015b).

Labelling everyone as *not well enough* raises the possibility that it will be hard to feel completely healthy for people who enter such management (Vogt et al., 2016). In the HPWP, all healthy individuals are at the same time reclassified as in need of medical attention *and* as actors with the possibility (and responsibility!) to "take action" to optimize their health. Thus, the *degree of medicalization* amounts to what can rightfully be called a social transformation (Flores et al., 2013). As envisioned, P4 medicine is a system that expects the active participation of the whole of society far beyond the current health system, a *health society* with social ties based on the common quest for health in networks of wellness-seeking individuals.

4.2. P4 values vs. people values

As we have argued throughout the paper, and as the HPWP illustrates, P4 medicine entails a number of factors that have been associated with an increasingly precarious balance of waste and harm in medicine. Among these are the use of new technology that allows more and more sensitive measurements of bodily factors, and the widened scope of medicine through an increasing focus in healthy people and health consumerism (Moynihan et al., 2012; Heath 2013, Hofmann 2014; Fisher & Welch, 1999; Callahan, 2008;Welch et al., 2011; Brodersen, 2014). Moreover, the aforementioned assumption that more screening is safer is currently encouraged through the promotion of P4 medicine that is also intertwined with commercial and academic interests (see below).

We have argued that P4 medicine is the, to date, most radical attempt to medicalize all aspects of human life (see also Vogt et al., 2016). P4 medicine is promoted as "holistic" in the sense that it goes beyond gene centrism and focuses on individual biomarkers at all levels, from molecules to personal characteristics, to social networks over time. Yet, to extent that it is holistic, it

represents a *techno-scientific* holism that widens and redefines health and wellness in quantitative terms in order to reimagine human bodies as control systems "which comply with medicine's fantasies of perfect management" (Tutton, 2014 p. 10, quoting Waldby 2000). Thus, the intensified focus on disease prevention through genetic testing, extensive (self-)monitoring and self-regulation promotes a certain view of health as largely knowable through and determined by biomarkers, but controllable through informed actions of the individual patient and precise treatments. It is in this context that proponents of P4 medicine want to extend the scope of measurements to also include the total "*exposome"* (Benson, 2016), *"sociometrics"* (Flores, 2013) and *social biomarkers* like social networks, religious commitmens, and general social behavior in the algorithms (Prainsack, 2014).[4] Whereas the inclusion of social aspects on one hand may be seen as an improvement in embracing human biocomplexity, and to humanize medicine, it raises concerns about the totality of "surveillance medicine" (Armstrong, 1995) and its capacity to turn the acknowledgement of "the human domain" into *even more* technoscientific control (Tutton, 2014;Vogt, 2016).

These aspects should be seen in connection to commercial and professional vested interests in P4 medicine. P4 research and funding opportunities are crucially dependent on patient participation to deliver the raw material for analysis, namely patient-specific data. Although the new preventive strategies are marketed as an open choice, emphasizing the ideals of patient autonomy and empowerment (Topol, 2012; Hood et al., 2015a), the intensified focus on disease risk in P4 medicine comes with encouragements that imply particular social norms about responsible citizenship. In this context it is pertinent to note how a large group of P4 medicine advocates find it necessary to stray very near coercion and placing imperatives on people's lives in order to reach their own goals: "patients must understand that it is their societal responsibility to make their anonymized data available to appropriate scientists and physicians so that the latter can create the predictive medicine of the future that will transform the health of their children and grandchildren" (Bousquet et al., 2011, p. 3). Similarly, it is equally pertinent to ask whether patients would be held responsible if they refuse to react to information on risk factors (MacArthur et al., 2013 p. 918). In the context of preventive medicine, risk

[4] One example of the use of social biomarkers is a pilot study where patients with bipolar disorder were monitored via their cell phones (Doryab et al., 2015).

becomes a central organizing principle for responsible personhood and citizenship (see also Schwennesen et al., 2008). Yet, whether the right decision for the *individual* is to make life style changes, undergo preventive treatments etc. is also a matter of complex issues relating to personal and social values. Thus, whether risk information is "actionable", but also whether it *should be*, are important questions to address from the outset.

At the same time as P4 medicine is promoted as a participatory and "democratic" solution to the increasing costs of the medical system, it is also promised as a foundation for a "wellness industry" that will provide economic growth. Here, an expanded scope of medicine means expanded markets. Compared to the wide-ranging ambitions, proponents of P4 provide relatively few self-critical assessments and often promise a revolution in healthcare that is predicted not to happen now, but at a time-point that is conveniently beyond critical scrutiny, typically designated as "the near future" or "in 5, 10 or 20 years time" (Flores et al., 2013; Hood et al., 2015; Topol, 2012, Vandamme 2013). Lofty visions may be important to motivate scientific endeavors. However, pushing the envelope through rhetoric may also create unwarranted expectations and divert precious resources from other potentially productive activities. 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*.

5. Conclusion

We are currently witnessing visions of an unsurpassed expansion in medicalization with intensive monitoring of healthy people, creating huge datasets of enormous complexity. At the same time, we are witnessing an increasing realization that the social aspects of human life – or *the human domain* – is of crucial importance for discussions of the prospects of preventive medicine.

To what extent, and how, P4 medicine will impact society and the socially embedded clinic remains an open question. Our intention has not been to dismiss its potential for improving biomedical research and public health.

Nevertheless, we have identified and analyzed tensions between the promise of *in silico* modelling of patient data and clinical *in socio* reality and discussed a number of concerns relating to personalized genomics and pilot projects for P4 medicine. The general problems facing preventive medicine in combination with the lack of evidence for the benefits and harms of P4 strategies make its proponents' optimistic promises particularly suspicious. No *in silico* model to date, no professional, and certainly not people themselves are currently able to handle the data deluge. P4 medicine is thus currently starting to create a clinical situation that it cannot handle itself, but that it nonetheless promotes as a solution and introduces to the clinic and people´s lives.

Moreover, the challenges of making people and society *participate* the way that the preventive strategies require are, although perhaps more banal than the scientific, maybe the most daunting. The lack of evidence that people react to risk information in the way that P4 proponents presuppose highlights a possible conflict between the professional ideal of P4 medicine and the social realm of human beings: Is risk information as "actionable" as assumed? Is health just one among many priorities for individuals? Just how far are we willing to go to achieve the goals of an optimal health? In this question, the conflict between the public´s idea of the ″good life″ and science´s definition of health will come to an ultimate test in P4 medicine.

In summary, based on the historical and current challenges of preventive medicine, we find that the burden of proof for the benefits of P4 medicine should weigh heavily on those who make the promises. So far, such evidence is very limited compared to the indications that P4 medicine will increase the problems with traditional preventive medicine. Having examined early results from the HPWP, we may still conclude as Khoury et al. (2012, p. 642) that the "lack of information on the clinical utility for most proposed P4 applications produces an evidence dilemma and a conundrum for implementation into practice". The high risk of unintentional harm and wasted resources raises an important question about the price we are willing to pay to explore the path of P4 medicine. In our view, until stronger evidence exists for health benefits and wider social implications, there are reasons to be highly skeptical of the promises of P4 medicine to offer society an economic boon and enable individuals to prevent future diseases.

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