# Innovation through Collaboration

## Interactive learning in nutrigenomics consortia

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**Innovation through Collaboration**

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Dit proefschrift werd mede mogelijk gemaakt met financiële steun van de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO) en de onderzoeksschool Wetenschap, Technologie en Moderne Cultuur (WTMC).

ISBN 978-90-6266-265-4

Graphic design, cover design and figures:
GeoMedia, Faculty of Geosciences, Utrecht University

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## Interactive learning in nutrigenomics consortia

**Samen werken, samen Innoveren**
*Interactief leren in nutrigenomics consortia*

(met een samenvatting in het Nederlands)

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op vrijdag 8 mei 2009 des middags te 12.45 uur

door

Laurentius Lysbertus Joseph Vandeberg

geboren op 18 oktober 1976 te Kerkrade

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# 1 Introduction



The emerging technology of nutrigenomics stimulates great expectations about future applications for personal health. Nutrigenomics is the study of the interaction between nutrition and the genome, and envisioned applications encompass nutrigenomics health tests, dietary services and so-called functional foods with an additional health promoting benefit (Ronteltap, van Trijp et al. 2007). These applications could for example be used in the prevention and treatment of genetically predisposed nutrition-related diseases like the Metabolic Syndrome. The Metabolic Syndrome is a combination of risk factors that eventually lead to cardio-vascular disease (Kahn, Buse et al. 2005). The Metabolic Syndrome begins with obesity. Obesity is responsible for 10-13% of deaths and 2-8% of health care costs in Europe, and is, therefore, *"one of the greatest public health challenges of the 21st century"* (www.who.int/nutrition/topics/obesity/en/index.html 17-11-2008).

Although nutrigenomics looks promising for consumers, patients and the health care systems as a whole, for the time being researchers are still in the process of unravelling the interaction between nutrition and the genome. For this research complementary knowledge from stakeholders with backgrounds in nutrition research, genetics research and the food industry has to be combined. Heterogeneous stakeholders have to interact in order to learn and innovate on the boundaries of these complementary knowledge pools. This so-called *interactive learning* is crucial for innovation in emerging technologies like nutrigenomics. The generation, combination and accumulation of knowledge might result in innovations: socially and/or economically successful applications of this knowledge in the form of products, services or processes.

The concept of interactive learning in innovation processes was introduced by Lundvall in 1985 (Lundvall 1985) who later defined interactive learning as *"a process in which agents communicate and even cooperate in the creation and utilisation of new economically useful knowledge"* (Lundvall, Johnson et al. 2002, p226). The positive influence of interactive learning on innovation has been acknowledged through different studies (e.g. (Von Hippel 1988; Lundvall 1992; Coombs, Green et al. 2001; Smits 2002; Moors, Enzing et al. 2003; Oudshoorn and Pinch 2003; Rohracher 2005; Smits and Hertog 2007; Boon, Moors et al. 2008; Moors, Boon et al. 2008; Smits and Boon 2008; Nahuis, Moors et al. 2009)). However, detailed insight into interactive learning itself is – still – lacking. At the same time, studies on interactive learning pre-dominantly focus on the outcome of the interactive learning process, rather than what learning is and how the outcomes are achieved (Meeus and Oerlemans 2005). As such, the interactive learning process can be seen as a black box. Consequently, there is the need for a framework for interactive learning in emerging technologies, focusing not only on the interactive learning outcome but also on the interactive learning process itself. Therefore, we want to know what interactive learning is and how it can contribute to the conceptualisation of innovation in emerging technologies.

In the next sections we take a closer look at the theoretical setting of interaction in emerging technologies (§1.1). The objective, focus, and relevance of our research are discussed in §1.2, which results in a central research question. In §1.3 we take a first look at the Framework for Interactive Learning in Emerging Technologies developed in this book. At the end of this introduction we present the outline (§1.4) and an overview of our publications that represent important building blocks of this book (§1.5).

## 1.1 Interaction in emerging technologies

Innovation is increasingly perceived as the collective effort of a variety of public and private stakeholders within the context of an innovation system. This also holds for the agri-food innovation system that developed into a *"heterogeneous, poly-disciplinary"* innovation system (Werrij 2007). The innovation system is a heuristic (Kuhlmann 2001) in which innovation is conceived as interactions of distinct actors (e.g. companies, market, government and supporting organisations), acquiring, understanding and combining knowledge and producing, diffusing, or using technologies, which result in the (re-)design of technical systems. *"[I]nnovation is a matter of producing new knowledge or combining existing elements of knowledge in new ways. It is thus, in the broadest sense, a 'learning process'"* (Edquist and Hommen 1999). Within innovation studies a broad variety of so-called User Producer Interaction (UPI) types focus on interactions between stakeholders in the innovation system. As it is not always clear what type of User Producer Interaction[1] is necessary in a particular context, Nahuis, Moors et al. (2009) developed a classification of contexts of User Producer Interaction in terms of the phase of technology development, the flexibility of the technology, and the heterogeneity of the stakeholder population. In emerging technologies like nutrigenomics, *interactive learning* between stakeholders is of special importance for the combination of complementary knowledge from heterogeneous stakeholders.

The diffusion (Rogers 1962) or technological performance (Foster 1986) of innovations can be depicted in an S-curve with various life stages (Tidd, Bessant et al. 2001). Technologies go through several life stages from invention (the original idea) to innovation (the successful economic and/or social application of the invention in a product, process or service). *"Emergence is the process or event of something coming into existence. For technological development this notion then relates to the very early stages of technological development."* (Van Merkerk and Van Lente 2005). Emerging technologies are characterised by the absence of a dominant design or definition, and (hardly) any commercially available applications (Utterback 1994). The emerging technology is surrounded with uncertainties and numerous open ends about future applications and related expectations (Nelson and Winter 1977). But, within the emerging technology there is a visible increase of linkages between stakeholders in the form of networks (Van Merkerk and Van Lente 2005). Stakeholders *"exchange*

1 E.g. demand articulation, user representation, learning by using and learning by interacting (Nahuis, Moors et al. 2009).

*knowledge in networks, because this is a way of sharing existing tacit knowledge, nurturing new knowledge, developing social capital and stimulating innovation*" (Van Rijnsoever, Hessels et al. 2008).

Knowledge is often still tacit in an emerging technology because not all new knowledge has been codified in e.g. scientific articles (Senker 1995; Arundel and Geuna 2004). Even when knowledge has been codified, it sometimes needs tacit explanation, for instance on how to perform experiments (Senker 1995; Howells 2002). Interactive learning facilitates the interchange and combination of complementary knowledge in codified and tacit form (Malmberg and Maskell 1999; Doloreux 2004). For stakeholders, interaction and collaboration is important because it is difficult for individual stakeholders to keep up with the rapid developments (Ponds 2008), especially in emerging technologies like nutrigenomics where complementary knowledge from nutrition and genomics has to be combined. The growth in scientific (sub)fields (Stichweh 1996) and interdisciplinary fields like nutrigenomics (Ponds 2008) has resulted in a division of highly specialised knowledge among heterogeneous stakeholders. The specialisation into (sub)fields has also resulted in more and more highly specialised instruments and research methods and has led to a further specialisation in know-how and expertise regarding these instruments and methods (Katz and Martin 1997). Related to the increase in specialisation are the increased costs for research. Thus, the combination of complementary specialised knowledge and research methods, and the combination of human resources and research funding, require the collaboration and interactive learning between stakeholders.

Interaction between stakeholders in an emerging technology is not only important for achieving scientific advancement. In the emerging phase, the technology is still 'fluid' and it is difficult for stakeholders to specify desired characteristics. When the technology becomes more 'solidified' due to increasing vested interests, stakeholders know far better what they want, but the options to intervene decrease. This trade-off is known as the Collingridge dilemma (Collingridge 1980). Therefore, interactive learning between stakeholders is also important for the co-construction and realisation of a shared vision among the stakeholders. Whereas knowledge is necessary to bring forth new product, process or service innovations, a shared vision can act as a driver and shared frame of reference for innovation (Checkland 1988; Vergragt 1988; Smits 2005).

To conclude, interactive learning is important in emerging technologies for the combination of resources and complementary (tacit) knowledge from heterogeneous stakeholders, for scientific advancement and the co-construction and realisation of a shared vision.

## 1.2 Objective, focus, relevance and central research question

Our research on interactive learning in nutrigenomics is part of the 'User-Producer Interaction in Functional Genomics Innovations' project, funded by the Societal Component of the Genomics Research Programme of The Netherlands Organisation

for Scientific Research[2]. Nutrigenomics is an emerging technology in which scientists are endeavouring to uncover the relation between nutrition and genes, through which new applications might be discovered. In their research, stakeholders from universities, research institutes and companies interact and exchange information and knowledge, and learn from each other. The stakeholders have organised their collaborations in nutrigenomics consortia, such as the Dutch Nutrigenomics Consortium and the German Competence Network Metabolic Syndrome. Therefore, the emerging technology of nutrigenomics, with its consortia in which heterogeneous stakeholders combine complementary codified and tacit knowledge, is thus suitable for studying interactive learning in emerging technologies.

Taking into account the importance of interactive learning in emerging technologies for innovation, and the lack of a satisfying model that takes both the outcome and the process of interactive learning into account, the main *objective* of this research is to understand interactive learning in emerging technologies. In order to reach this objective we first develop a Framework for Interactive Learning in Emerging Technologies (FILET) based on a broad set of innovation literature about interactive learning. For the exploration of the FILET we *focus* on interactive learning between heterogeneous stakeholders in nutrigenomics consortia.

The *scientific relevance* of this research is our contribution to the conceptualisation of interactive learning. Our findings provide insight into innovation processes of emerging technologies (such as nutrigenomics) in which complementary knowledge from heterogeneous stakeholders has to be combined in order to innovate. This explorative research into interactive learning in emerging technologies has direct *societal relevance*. The conceptualisation of interactive learning in emerging technologies increases our understanding of the interactive learning process and how it influences the interactive learning outcome. This insight provides starting points for recommendations that might stimulate interactive learning. In the case of nutrigenomics the insights into interactive learning might stimulate the elucidation of important relations between nutrition and the genome. This could contribute to service and product innovations that promote health and prevent diseases, for example in the area of the Metabolic Syndrome.

Following the abovementioned objective, focus and relevance of our research, we formulate the *central research question*:

*How can interactive learning in emerging technologies be conceptualised, and how can this conceptualisation provide insights into interactive learning between heterogeneous stakeholders in nutrigenomics?*

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2 *"The MCG programme is a joint programme of the Netherlands Organization for Scientific Research (NWO) and the Netherlands Genomics Initiative (NGI). The programme was started in 2002 to formulate and develop the social component of the genomics-research."* (www.mcgprogramme.nl 1-8-2008) (project number MCG 050-32-550)

In order to answer this leading research question the research is divided into two parts. First, we develop a Framework for Interactive Learning in Emerging Technologies. Second, we explore the FILET in real life situations of interactive learning in nutrigenomics. For the exploration part we perform case studies of nutrigenomics consortia. In the next section we take a first look at the framework we develop in this book.

## 1.3 Framework for Interactive Learning in Emerging Technologies

In Chapter 2 we develop the Framework for Interactive Learning in Emerging Technologies (FILET) starting from the basic characteristics of interactive learning. Interactive learning is a process with an outcome (Meeus and Oerlemans 2005). The outcome of interactive learning processes in emerging technologies becomes perceptible in scientific publications, patents and in an increase in tacit knowledge. At the same time, a shared vision among the complementary heterogeneous stakeholders is being co-constructed and realised. In our research we are not only interested in the outcome but also in the opening of the black box of the interactive learning process itself. Stakeholders interact and exchange knowledge within the interactive learning process. Therefore, the first two building blocks of the FILET are the interactive learning *outcome* and the interactive learning *process*. The interactive learning process itself can be influenced by conditions that enable or constrain the interactive learning process. For example, in order to exchange complementary and often tacit knowledge, stakeholders have to interact face-to-face. Therefore, geographical proximity is regarded as an essential condition for interactive learning. Recently, other dimensions of proximity (e.g. cognitive and regulatory) are also regarded as important for interactive learning. Therefore, we take these *conditions* into account when constructing the FILET. The conditions that influence the interactive learning process constitute the third building block of the FILET. The outcome, process and conditions are the three building blocks we start with for the construction of the FILET (Figure 1).

## 1.4 Outline and research questions

In the first part of this book we develop a Framework for Interactive Learning in Emerging Technologies. This framework is then explored in case studies, focusing on consortia around the emerging nutrigenomics technology. To link these two parts we take a closer look at nutrigenomics in an 'intermezzo'.

In Chapter 2 we develop the Framework for Interactive Learning in Emerging Technologies. We start with the outcome of interactive learning before turning to the

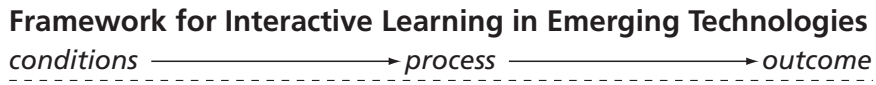


**Figure 1** Building blocks of the Framework for Interactive Learning in Emerging Technologies

interactive learning process itself and the conditions that influence the interactive learning process. For the development of the FILET, we formulate the following *sub-questions*:

1. *What is the outcome of the interactive learning process in emerging technologies?*
2. *What are the elements of the interactive learning process and how do they influence the interactive learning outcome?*
3. *What are the conditions for interactive learning and how do they influence the interactive learning process?*

In order to explore the developed FILET in real life circumstances we will perform case studies of interactive learning in nutrigenomics. Before turning to the case studies we first take a closer look at the emerging technology of nutrigenomics. In Chapter 3 we describe the state of the art and expectations of nutrigenomics. We use patent and publication analyses to sketch the development of nutrigenomics over time and to assess if nutrigenomics is an interesting emerging technology for the exploration of the FILET. In this chapter it becomes clear that nutrigenomics is a 'hot spot', an interesting new, emerging field, surrounded by expectations such as personalised nutrition, functional foods and a potential solution to food-related health care problems. For this exploration we formulate the following *sub-questions*:

4. *What is nutrigenomics and what are the expectations surrounding nutrigenomics?*
5. *Is the emerging technology of nutrigenomics a hot spot?*

Chapter 4 presents an overview of the methodology used in chapters 2 and 3. The main part of this chapter deals with the case study method used for the exploration of the developed FILET. We explain why the case study is the preferred research method, we develop selection criteria for case studies and select cases from a list of candidate cases. For the actual studying of the cases we present an analytical framework, for which the theoretical concepts of the FILET are operationalised into empirical variables.

Chapters 5 and 6 report on the two selected case studies of the Dutch Nutrigenomics Consortium and the German Competence Network Metabolic Syndrome respectively. Each chapter gives a general introduction of the consortium, plus an analysis of interactive learning within the consortium using the analytical framework. The findings are summarised in the last section of these chapters. To steer the case studies we formulate the following *sub-questions*:

6. *What was the interactive learning outcome of the consortium?*
7. *How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process?*
8. *How were the elements of the interactive learning process influenced by the conditions for interactive learning?*

Finally, the central question of the research is answered in Chapter 7. We draw conclusions at the aggregate level through which we can assess the validity of the FILET. The insights that result from the development and exploration of the FILET can be used to make recommendations for further research and for the stakeholders and policy makers who want to stimulate innovation in emerging technologies. Therefore, at the end of our research we will answer the following *sub-question*:

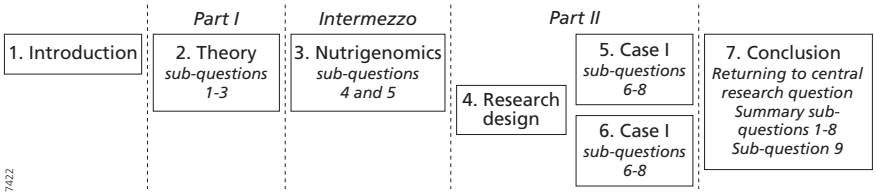


**Figure 2** Book outline: chapters and answers to (sub-)questions

9. *Which lessons can be drawn for future research on interactive learning in emerging technologies, and which recommendations can be made to stakeholders and policy makers who would like to stimulate interactive learning and innovation in emerging technologies?*

The outline of this book and the chapters in which the sub-questions are answered is visualised in Figure 2.

## 1.5 Publications

This book is one of the codified outcomes of the research into interactive learning in the emerging technology of nutrigenomics. It provides a complete overview of the research. Earlier versions of (parts of) individual chapters have already been published.

Moors, E. H. M., W. P. C. Boon, R. Nahuis, R.L.J. Vandeberg. (2008). *"User-Producer Interactions in Emerging Pharmaceutical and Food Innovations."* International Journal of Innovation Management – Special issue on User Innovation 12(3): 459-487.

Van Rijnsoever, F. J., L. K. Hessels, R.L.J. Vandeberg. (2008). *"A resource-based view on the interactions of university researchers."* Research Policy 37(8): 1255-1266.

Vandeberg, R. L. J. and W. Boon (2009). *"Identifying Innovation Hot Spots in Genomics."* Genomics, Society and Policy.

Vandeberg, R. L. J. and E. H. M. Moors (2008). *"A Framework for Interactive Learning in Emerging Technologies."* Innovation Studies Utrecht (ISU) Working Paper Series #08.06.

Vandeberg, R. L. J. and E. H. M. Moors (under review). *"A Framework for Interactive Learning in Emerging Technologies."* Journal of Technological Forecasting and Social Change.

Other publications that are related to the subject of this book but did not become part of this book are:

Vandeberg, R. L. J. (2005). *Open innovatie: de innoverende gebruiker.* Open stellingen – Essays over Open innovatie. Den Haag, Adviesraad voor Wetenschaps- en Technologiebeleid: 41-47.

Vandeberg, R. L. J. and J. H. A. M. Rodenberg (forthcoming). "White Paper Intelligence Driven Innovation." www.kennisportal.com.

# 2 Towards a Framework for Interactive Learning in Emerging Technologies



One of the goals of our research is to develop a framework that helps us to conceptualise and understand interactive learning in emerging technologies. The development of such a framework is important because the concept of interactive learning was already introduced in the 1980s by Lundvall[3] (1985) who stressed the importance of interactive learning for innovation, but elaborate studies into interactive learning are lacking. Most research on interactive learning only focuses on the outcome (Meeus and Oerlemans 2005), whereas interactive learning is a process with an outcome. Consequently, the interactive learning process is a black box. We attempt to open this black box in our framework because it might provide insights into the interactive learning process itself and how it influences the outcome. In this chapter, therefore, we answer the first part of our *central research question*:

***How can interactive learning in emerging technologies be conceptualised**, and how can this conceptualisation provide insights into interactive learning between heterogeneous stakeholders in nutrigenomics?*

In the following sections we build the Framework for Interactive Learning in Emerging Technologies (FILET) starting out from the three building blocks we identified in the Introduction (§1.3). Interactive learning is a process with an outcome, and the process is influenced by conditions (Figure 3). Since most learning research focuses on the outcome we first describe the interactive learning outcome (§2.1). We then open the black box of the interactive learning process by describing the elements of the interactive learning process (§2.2) and propose relations between the interactive learning process and the interactive learning outcome (§2.3). We then turn to the conditions for interactive learning (§2.4) and propose relations between the conditions for interactive learning and the interactive learning process (§2.5). At the end of this chapter we present the complete Framework for Interactive Learning in Emerging Technologies (Figure 7).

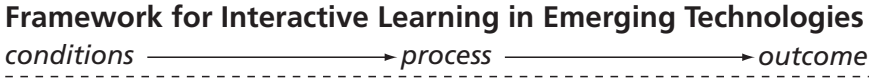


**Figure 3** Building blocks for a Framework for Interactive Learning In Emerging Technologies

3 Lundvall's exact wording: *"learning-by-interacting"* (Lundvall 1985).

## 2.1 Interactive learning outcome

In relation to learning and learning outcomes, the concepts of first and second-order learning are often used (Argyris and Schön 1978)[4]. First-order learning refers to instrumental knowledge, which is specific knowledge for solving a problem that *"relate[s] to the cognitive level of analysis"* (Kerkhof and Wieczorek 2005) within an existing framework. Instrumental scientific knowledge (i.e. first-order learning) provides answers to unknowns and solutions to specific problems. Second-order learning refers to conceptual knowledge related to the framework itself and the shared vision among stakeholders of this framework, and *"involve[s] the modification of an organisation's underlying [..] objectives"* (Argyris and Schön 1978, p3). In second-order learning stakeholders explore the framework and question underlying assumptions about the specific problems within it. A shared vision entails the *dominant problem definition* (Vergragt 1988), *common goal* (Checkland 1988; Vergragt 1988; Smits 2005), *objectives* (Argyris and Schön 1978, p3) and the *approach* taken to realise them. For example, the problem might be concerned with a nutrition-related genetically predisposed disease and the goal of the consortium might be to find a solution to that problem. The objectives that the consortium set itself contribute to the fulfilment of the goal. Therefore an approach might be arranged in the form of a division of labour/research among the stakeholders. The shared vision is co-constructed by the stakeholders at the beginning of collaboration and during the research collaboration does it become evident to what extent the stakeholders can realise the shared vision: can the goal actually be addressed with the emerging technology, can the objectives the stakeholders set for themselves be reached, and does the approach lead to the envisioned results? The co-construction and realisation of a shared vision is an 'innovation journey' (Van de Ven, Douglas E. Polley et al. 1999) which starts *"with the identification of an opportunity"* (Rip 2008). Through the journey the stakeholders can further articulate, change and realise (part of) their shared vision due to new insights they gain during the interactive learning process.

Since we are specifically interested in knowledge that results from the interactive learning between stakeholders[5] we use the term *interactive scientific knowledge outcome* in order to indicate the instrumental scientific knowledge (i.e. first-order learning outcome) that results from the interactive learning process. In order to capture the shared vision that is co-constructed by the stakeholders at the beginning of the collaboration and the extent to which the stakeholders realise the shared vision, we use the term *realisation of the shared vision* for the second-order learning outcome of the interactive learning process.

Knowledge, whether in the form of interactive scientific knowledge outcome or the realisation of a shared vision, has a codified and a tacit dimension. Tacit knowledge

4 Others terms for first-order learning are instrumental learning, single-loop learning, or lower-order learning; other terms for second-order learning are political learning, double-loop learning, or higher-order learning (see Kerkhof and Wieczorek (2005) for an overview).

5 Stakeholders might also create valuable knowledge on their own, for which interaction in a consortium was not necessary (e.g. through internal R&D projects).

is knowledge that exists in individuals, and codification is the reduction of tacit knowledge into symbolic representations (e.g. scientific articles, patents or standards) (Johnson, Lorenz et al. 2002). In science, knowledge is normally diffused in codified form by means of articles. However, in an emerging technology there is a latency time between discovery in a laboratory and codification in an article (Arundel and Geuna 2004). Therefore, relevant knowledge might not yet have been codified, as for example Senker (1995) found in her case studies on the role of tacit knowledge in innovation: *"many of the researchers [report] that most of the underlying knowledge has not yet been published or documented anywhere"*. But even when new scientific knowledge has been codified in articles, tacit knowledge is still an important factor in interactive learning because scientific codified knowledge can be so complex that it needs tacit know-how for interpretation and assimilation (Howells 2002). The importance of tacit knowledge in science is also stressed by Senker (1995) who refers to the apprenticeship and craftsmanship of scientists, entailing important know-how that cannot be codified (e.g. how to write articles): *"[G]enetic engineering techniques continue to incorporate many empirical and tacit elements; even in the more codified microbial systems, it is not always possible to specify precisely which gene fragment will be spliced or, where this is possible, to explain why a particular set of procedures produces a specific effect"* (Senker 1995). Tacit knowledge itself entails both i) knowledge that might not yet have been written down (i.e. codified) and ii) knowledge that is important but difficult to codify. Polanyi's (1983[1966], p4) statement *"we know more than we can tell"* refers to particular knowledge of which we might not be aware that it is important or valuable to others and which cannot be codified. Especially tacit knowledge consisting of habits, culture, values and norms is often not recognised by individuals as being important knowledge for realising a shared vision that stimulates innovation. It is this tacit knowledge that can only be transferred through face-to-face contact (Malmberg and Maskell 1999; Doloreux 2004). "*While explicit [i.e. codified] knowledge can be shared by language and written documents, the transfer of tacit user knowledge requires face-to-face interactions*" (Lettl 2007).

***In summary***

The outcome of interactive learning is twofold, namely *interactive scientific knowledge outcome* and the *realisation of a shared vision*, which both have a tacit and codified dimension (Figure 4). Tacit and codified knowledge are complementary dimensions, especially in emerging technologies: First, not all scientific knowledge that can be codified might already have been codified in articles and is still tacit. Second, codified knowledge is often so complex that it needs further tacit explanation for interpretation and assimilation. Third, not all knowledge can be codified and tacit knowledge is important because it entails habits, culture, values and norms that are crucial for the realisation of a shared vision.

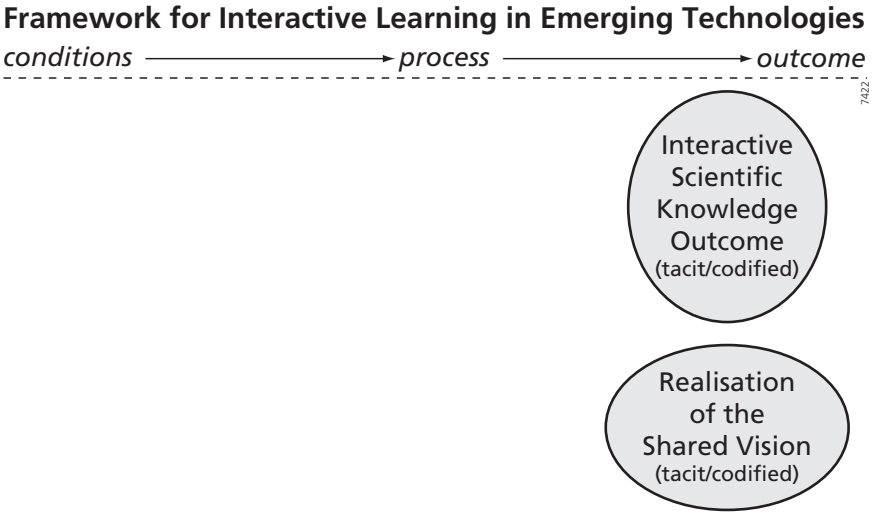


**Figure 4** Interactive learning outcome

## 2.2 Interactive learning process

In this section we start to open the black box of the interactive learning process and identify the elements that describe the interactive learning process in emerging technologies. Lundvall's (1988) definition of interactive learning provides a good starting point for the interactive learning process building block of our FILET. From the definition -*"a process in which agents communicate and even cooperate in the creation and utilisation of new economically useful knowledge*" (Lundvall, Johnson et al. 2002, p226) – it is evident that there has to be a setting in which interaction between agents is possible. In emerging technologies this setting for interactive learning is not yet automatically in place. Leeuwis et al. (2005) refer in their work to the process of *network formation*. According to Hekkert et al. (2007) *"[n]etwork activity can be regarded as a precondition to 'learning by interacting'"*.

For the formation of a network that can function as the setting for interactive learning, a network builder (Kamp 2002) or *prime mover* (Smits and Kuhlmann 2004; Leeuwis, Mierlo et al. 2005) plays an important role. The prime mover takes the initiative to bring complementary stakeholders together. The initiative of the prime mover is driven by a sense of urgency and mutual dependency. The sense of urgency refers to a problem perceived by the prime mover and the possibilities the emerging technology might provide to address this problem according to the prime mover. For example, the prime mover might notice an increase in the prevalence of nutrition-related genetically predisposed diseases that could be prevented or treated with applications resulting from nutrigenomics research. In emerging technologies, where complementary knowledge from heterogeneous stakeholders has to be combined, there exists a mutual dependency on complementary knowledge and resources

between stakeholders. In the case of nutrigenomics, developments are dependent on the combination of knowledge from nutrition and genomics, the expertise of several 'omics' research methods[6], and resources such as research facilities and funds.

When heterogeneous stakeholders combine complementary knowledge they might not be able to fully 'understand' the knowledge brought in by other stakeholders. Interactions between these stakeholders with their different backgrounds can be facilitated by *intermediaries* (Bunders, Broerse et al. 1999; Moors, Enzing et al. 2003; Boon 2008; Boon, Moors et al.; Moors, Boon et al. 2008). An intermediary organisation *"connect[s], translate[s] and facilitate[s] flows of knowledge"* (Van Lente, Hekkert et al. 2003) or is, as Howells states, *"an organisation or body that acts [as] an agent or broker in any aspect of the innovation process between two or more parties"* (Howells 2006). An intermediary could then be regarded as a broker between stakeholders in order to create mutual understanding and bridge a – potential – gap between different scientific disciplines (Geurts 1993). In order to clearly distinguish the intermediary from the prime mover who perceives a sense of urgency and 'connects' the stakeholders into a network, the intermediary translates knowledge from one stakeholder to another (Geurts 1993).

Within the network of stakeholders, knowledge is interchanged and assimilated in order to learn and innovate. Therefore, the *knowledge flows* between the stakeholders are important in the interactive learning process. The taxonomy of knowledge provided by Lundvall and Johnson (1994) can be used as a heuristic tool to distinguish several forms of knowledge that can be interchanged between stakeholders. *Know-what* knowledge refers to facts (e.g. the ingredients of a product), *know-why* refers to knowledge on scientific principles and laws (e.g. heredity principles), *know-how* refers to the skills or the ability to do something (e.g. an experiment), and *know-who* refers to who has which (of the aforementioned types of) knowledge. According to Lundvall, in the learning economy know-who and know-how are becoming more important because of the *"general trend towards a more composite knowledge base"* (Lundvall 2006), for which complementary knowledge from different stakeholders is needed. In science-based developments the know-how of scientists becomes very important (Polanyi 1958; Ziman 1979). In order to combine this know-how that is dispersed over different stakeholders, stakeholders start to cooperate in consortia (Johnson, Lorenz et al. 2002).

***In summary***

Starting from the literature on interactive learning we identified four elements of the interactive learning process: *prime mover, intermediary, network formation* and *knowledge flows*. Based on their heterogeneity they can be subdivided into two 'classes': the prime mover and intermediary are specific stakeholders that can be organisations and/or individuals, and the network formation and the knowledge flows are procedural elements of the interactive learning process.

6 We elaborate on the knowledge and research methods involved in nutrigenomics research in Chapter 3.

## 2.3 Relations between the interactive learning process and the interactive learning outcome

Interactive learning is a process with an outcome. As elements of the interactive learning process we identified the *prime mover, network formation, intermediary* and the *knowledge flows* between the stakeholders (§2.2). These elements are of influence on the interactive learning outcome (i.e. *interactive scientific knowledge outcome* and *realisation of the shared vision*) (§2.1). However, in the literature, relations between the elements of the interactive learning process and the interactive learning outcome are seldom highlighted. Based on our literature review we can propose relations between the elements of the interactive learning process and the interactive learning outcome.

Relations between the elements of the interactive learning process and the interactive scientific knowledge outcome:

- The network builder or *prime mover* starts the network formation. Driven by a sense of urgency the prime mover seeks collaboration with other stakeholders. This collaboration becomes necessary when stakeholders are mutually dependent on their complementary resources (e.g. knowledge, research facilities and funds). In emerging technologies where complementary knowledge needs to be combined, network formation brings complementary stakeholders together. As such, it is assumed that *network formation* influences the scientific knowledge outcome because it creates the setting for the combination of complementary knowledge (tacit and codified).
- The knowledge flows between the stakeholders contain know-what, know-why, know-how, and know-who knowledge. This knowledge creates instrumental scientific insight into the emerging technology (i.e. first-order learning). It is assumed that the *knowledge flows* between the stakeholders eventually accumulate into the interactive scientific knowledge outcome, e.g. scientific articles and an increase in tacit know-how.
- Knowledge flows between stakeholders are the result of a difference in the required complementary knowledge that is dispersed among the stakeholders. The combination of different knowledge might lead to new insights and innovation. However, the differences between knowledge fields might be so great that an intermediary is necessary to bridge the knowledge gap. Therefore it is assumed that an *intermediary* enables the combination of complementary knowledge from different knowledge fields, which results in an interactive scientific knowledge outcome. The intermediary is able to do this because his expertise has similarities with the knowledge fields that have to be combined. Therefore, the intermediary is able to understand the knowledge from the different knowledge fields and translate that knowledge so that it becomes comprehensible for other stakeholders.

Relations between the elements of the interactive learning process and realisation of the shared vision:

- The prime mover takes the initiative for a collaborative effort in the emerging technology. This initiative is driven by a sense of urgency and mutual dependency. The sense of urgency emerges from the problem as perceived by the prime mover and the possible solutions that might ensue from the emerging technology. As

such, the sense of urgency provides a starting point for a shared vision. Therefore, it is assumed that a *prime mover* initiates the formation of a shared vision, both tacit and codified.

- During the *network formation* the stakeholders can evaluate the vision that is propagated by the prime mover. At the same time the vision of the prime mover can be adapted in order to incorporate the individual visions of the complementary stakeholders. It is assumed that the network formation results in a shared vision among the stakeholders. As such the shared vision is co-constructed by the stakeholders during network formation. This is important for interactive learning because a shared vision sets a common goal for the stakeholders and generates a shared frame of reference through which innovation is stimulated (Checkland 1988; Vergragt 1988; Smits 2005).
- During the co-construction and realisation of a shared vision, an *intermediary* might function as a bridge between stakeholders that have competing visions in order to achieve a shared vision in the end. Consequently it is assumed that the intermediary influences the co-construction and realisation of a shared vision.
- It is assumed that realisation of the shared vision is influenced by the *knowledge flows* between the stakeholders during the actual research. New scientific findings (first order) result in new insights, through which the stakeholders might change the original shared vision (second order). This can result in a shift or change of the shared vision (e.g. in the goal or the approach taken to reach the goal). For example, it might be found that the expectations surrounding the emerging technology cannot be fulfilled. Therefore, the emerging technology cannot (yet) provide the solutions to the perceived problems that were envisioned at the beginning of the collaboration.

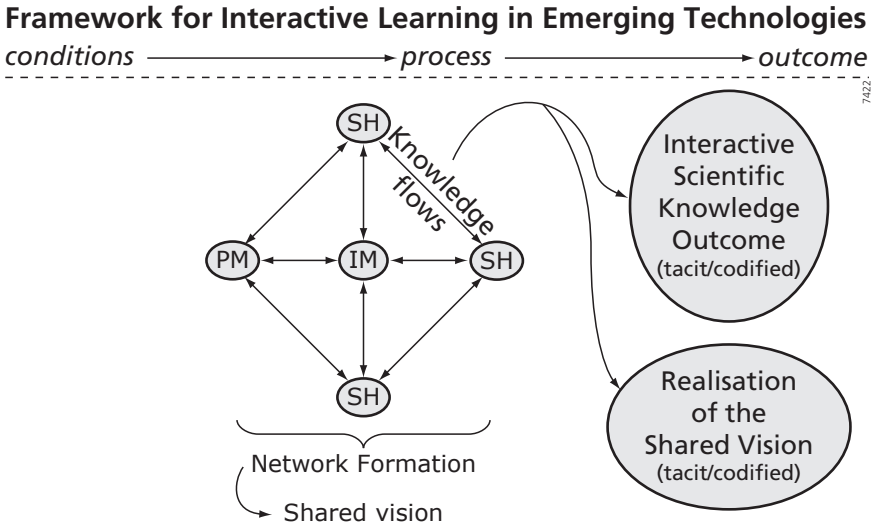


**Figure 5** Relation between elements and outcome of interactive learning (PM=prime mover; IM=intermediary; SH=other stakeholders in network)

***In summary***

We have focused on the *prime mover, network formation, intermediary* and the *knowledge flows*, and how these elements of the interactive learning process influence the interactive learning outcome. Based on these elements, we can further detail the Framework for Interactive Learning in Emerging Technologies (Figure 5). In the next section we focus on the third building block of the framework: the conditions for interactive learning.

## 2.4 Conditions for interactive learning

In this section we turn to the conditions for interactive learning. We are specifically interested in interactive learning in emerging technologies. In emerging technologies knowledge is often still tacit (Arundel and Geuna 2004). Moreover, codified (scientific) knowledge can be so complex that it needs tacit know-how for interpretation and assimilation (Howells 2002). At the same time, tacit knowledge that encompasses habits, culture, values and norms is often not recognised by individuals as being important knowledge for e.g. co-constructing and realising a shared vision that stimulates innovation. It is this tacit knowledge that can only be transferred through face-to-face contact (Malmberg and Maskell 1999; Doloreux 2004). In this setting *geographical proximity* is a key concept because geographical *proximity* facilitates face-to-face meetings in which tacit knowledge can be exchanged and combined (Feldman 1994; Gertler 2003). In the recent decade, proximity has been a prominent concept within several fields such as inter-organisational collaboration (e.g. (Sternberg 1999)), innovation (e.g. (Oerlemans, Meeus et al. 2001)) and regional economic development (e.g. (MacKinnon, Cumbers et al. 2002)). As such, proximity is *"an important emerging concept in several fields of science, for example in innovation studies"* (Knoben and Oerlemans 2006).

Traditionally, *geographical proximity* is regarded as the dominant enabling condition for interactive learning and innovation because geographical proximity enables face-to-face meetings which facilitate the exchange of tacit and complex knowledge. Since the beginning of this century scholars have questioned the importance of geographical proximity for interactive learning (e.g. (Breschi and Lissoni 2001; Howells 2002; Malmberg and Maskell 2002; Gertler 2003; Boschma 2005; Torre and Rallet 2005)). It has been argued that geographical proximity may facilitate interactive learning *"but it is neither a necessary nor a sufficient condition"* (Boschma 2005). Therefore, other dimensions of proximity are also expected to influence interactive learning and innovation. For example, *"cognitive proximity among researchers is required for meaningful communication in research projects"* (Ponds, Oort et al. 2007). In his seminal article on proximity and innovation, Boschma (2005) distinguishes four dimensions of proximity besides geographical proximity: cognitive proximity, institutional proximity, social proximity and organisational proximity. *"What unites these different dimensions of proximity is that they reduce uncertainty and solve the problem of coordination, and, thus, facilitate interactive learning and innovations"* (Boschma 2005). Before we elaborate on the different dimensions of proximity, we must first address two issues:

1. *Institutional proximity* covers both formal rules and regulations like laws and mutual agreements, and informal rules like working habits and norms. Institutional proximity may encourage or hamper interactive learning between stakeholders (Lundvall 1992; Feldman 1994; Boschma 2005). *"As such, institutions are enabling or constraining conditions that affect the level of knowledge transfer, interactive learning, and (thus) innovation*" (Boschma 2005). In order to make a clear distinction between formal and informal rules, we refer to *regulatory proximity* (i.e. formal rules) and *cultural proximity* (i.e. informal 'unwritten' rules (Ponds, Oort et al. 2007)). By making this distinction we deviate from the division in dimensions of proximity in Boschma's (2005) work. We do this because it allows us to distinguish formal from informal rules, which might provide us with more detailed insights into interactive learning.
2. For the analysis of the dimensions of proximity different levels can be distinguished (Knoben and Oerlemans 2006). The micro level refers to the individual level (i.e. individual stakeholders); the meso level refers to the network level (e.g. a network of stakeholders); and the macro level refers to the innovation system. The relation the research focuses on determines the level of analysis. We are interested in interactive learning between stakeholders that form networks in emerging technologies. Therefore, the level of analysis in our research is the meso level for all dimensions of proximity. We make one exception for regulatory proximity, for which we focus both on the meso and macro level, given that collaboration in emerging technologies can also be influenced by regulations at the macro level.

Table 1 summarises the definitions of the dimensions of proximity used by Boschma and also shows the distinction we make in institutional proximity. In the remainder of this section we focus on *geographical, cognitive, regulatory, cultural, social* and *organisational proximity*.

**Table 1** Boschma's (2005) dimensions of proximity and definitions (taken from (Collins and Vecci 2005), adapted by RV, page numbers refer to the pages in (Boschma 2005)).

| Proximity | Definition |
|---|---|
| Geographical | The spatial or physical distance between economic actors, both in its absolute and relative meaning. p.69 |
| Cognitive | A firm's 'cognitive base should be close enough to the new knowledge in order to communicate, understand and process it successfully' p.63 |
| Institutional<br>• Regulatory<br>• Cultural | Following the distinction between formal and informal institutions, the notion of institutional proximity includes both the idea of economic relations between actors sharing the same institutional rules of the game [i.e. regulatory proximity – RV], as well as a set of cultural habits and values [i.e. cultural proximity – RV]. A common language, shared habits, a law system securing ownership and intellectual property rights, etc., all provide a basis for economic coordination and interactive learning. p.68 |
| Social | Relations between actors are socially embedded when they involve trust, based on friendship, kinship and experience. Accordingly, the definition of social proximity does not include situations in which people share sets of values, such as ethnic and religious values. p.66 |
| Organisational | The extent to which relations are shared in an organisational arrangement, either within or between organisations. To be precise, this involves the rate of autonomy and the degree of control that can be exerted over arrangements. p.65 |

***Geographical proximity***

*Geographical proximity* is the absolute or relative spatial or physical distance between stakeholders (Boschma 2005)[7]. This is an important condition for interactive learning since it facilitates face-to-face contacts (Feldman 1994; Gertler 2003). As we have seen, in emerging technologies the exchange of complex complementary scientific knowledge is often still tacit and the co-construction and realisation of a shared vision among the heterogeneous stakeholders is fundamental to innovation. The more complex the interchanged knowledge (both scientific knowledge as well as the shared vision), the richer the 'medium' to exchange the knowledge should be. Richness is a gliding scale for 'media', which depicts the extent to which the medium meets the complexity of the interchanged knowledge. The media richness is based on four properties (Fulk and Steinfield 1990):

1. The speed of feedback;
2. The number of cues (e.g. verbal and non-verbal cues);
3. The richness of the language that can be used; and
4. The public or private character of the information (i.e. the accessibility of information).

Based on these properties and the complexity of the interchanged knowledge, a scale can be constructed (Bongers 2000) (Figure 6).

7 Absolute being the distance that has to be covered (e.g. in kilometres) and relative the 'costs' involved to cover that distance (e.g. travelling time) (Collins and Vecci 2005).

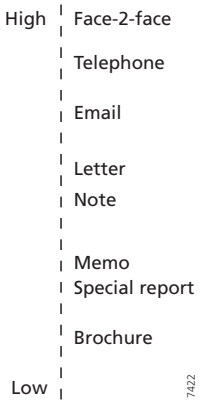


**Figure 6** Relation between media richness and knowledge complexity (based on (Bongers 2000, p.65))

Face-to-face communication is the richest medium and is therefore crucial for interactive learning in emerging technologies in which tacit knowledge is interchanged (Malmberg and Maskell 1999; Doloreux 2004). Face-to-face interactions are facilitated by geographical proximity.

Since the rapid diffusion of ICT it has been claimed that not only codified knowledge can be transferred over geographical distance and through time by all means of communication devices (Koschatzky, Kulicke et al. 2001), but also tacit knowledge through video conferencing for instance. However, several studies have falsified this so-called 'death of distance' hypothesis (e.g. (Blasio 2006)). This does not automatically imply that constant geographical proximity is required. Also 'temporary' geographical proximity can facilitate those moments when tacit knowledge can be interchanged and combined (e.g. (Gallaud and Torre 2005; Hyypiä and Kautonen 2005; Torre and Rallet 2005; Torre 2008)). Temporary geographical proximity might also circumvent the negative effects of too close geographical proximity. If stakeholders are located too near to one another they can also 'learn' from each other by simply *"monitor[ing] each other constantly, closely, and almost without effort or cost"* (Malmberg and Maskell 2002). This opportunistic behaviour has a negative effect on the collaboration between these stakeholders. Another negative effect of geographical proximity might be lock-in; if organisations only look inside their own geographical boundaries, they might fail to identify new opportunities that arise in organisations outside the agglomeration (Boschma 2005).

### *Cognitive proximity*

C*ognitive proximity* denotes a common knowledge base and/or expertise, which enables people or organisations to learn from each other (Boschma 2005). Cognitive proximity is the distance/closeness between stakeholders within the network with respect to an individual's education, interest and working experience and the technological focus of the organisation. Learning is a cumulative, path-dependent process leading to asymmetric resources and competences of stakeholders (Dosi 1997). The difference between stakeholders' resources and competences creates a

potential for learning (Schumpeter 1934; Cohen and Levinthal 1990; Kogut and Zander 1992; Sapienza, Parhankangas et al. 2004). In general, stakeholders will look for new knowledge in *"close proximity"* (Boschma 2005), because then it is expected that they will be able to assimilate new knowledge from other stakeholders and bridge the knowledge gap. Searching in close cognitive proximity often results in cumulative localised outcomes with a high degree of tacit knowledge (Cohendet and Llerena 1997; Nooteboom 1999; Boschma 2004). If all organisations look for new knowledge at close proximity, different knowledge will be dispersed over different organisations (Antonelli 1995). Interactive learning is dependent on combining new and/or existing complementary knowledge of heterogeneous stakeholders (Nooteboom 2000). It is not easy to incorporate external knowledge into one's own knowledge system. Therefore, the cognitive distance should not be too large (Cohendet and Llerena 1997; Boschma and Lambooy 1999) and a certain amount of absorptive capacity is needed in order to cross a potential knowledge gap. Absorptive capacity is the ability of organisations to recognise the value of new, external knowledge, to assimilate it, and to apply it to commercial ends which is critical to its innovative capabilities (Cohen and Levinthal 1990). For example, cognitive proximity between scientists is relatively high *"due to the use of a common codebook"* (Ponds, Oort et al. 2007).

At the same time, some cognitive distance is required since too close cognitive proximity can lead to a *"cognitive lock in [..] obscur[ing] the view on new technologies or new market possibilities"* (Boschma 2005), which is also known as the *"competency trap"* (Levitt and March 1996, p519). Hence, contacts with heterogeneous information sources and openness are important (Saviotti 1996). Another argument for keeping some cognitive distance is that organisations with close cognitive proximities (often competitors) are very reluctant to share knowledge with each other, because it might lead to unwanted spill-overs (Cantwell and Santangelo 2002); organisations could learn from competitors at close cognitive distance without undertaking internal R&D merely by copying successful strategies.

#### *Regulatory proximity*

*Regulatory proximity* in this study is related to the formal regulations that influence the stakeholders. For regulatory proximity two levels of analysis are distinguished. We make a distinction between the meso and macro level: the meso level refers to the network of heterogeneous stakeholders and formal agreements between these stakeholders; the macro level refers to regulations at the innovation system level.

Regulations at the *macro level* are important factors for innovation (Schellekens 2008). These regulations the macro level can (partly) reduce the uncertainty that surrounds emerging technologies. Regulations can create a niche market or protected market space for emerging technologies. This reduces the uncertainty of return on investments. For example, new regulations will only allow so-called functional foods onto the EU market if their health claim is supported by scientific insight. Nutrigenomics research can provide science-based evidence for functional foods. This might provide stakeholders with a certain degree of certainty about the future market for their applications, which does create some prospects in terms of return on investments. The outlook regarding return on investment stimulates stakeholders to invest in emerging technologies. In emerging technologies the availability of government funding can also be regarded as a regulation that stimulates R&D (Autio,

Kanninen et al. 2008). This government funding is important for the development of the emerging technology because often (basic) research is performed by research institutes that are largely dependent on funding during the emergent phase. Government funding also stimulates costly, risky and long-term research, upon which a single stakeholder would seldom embark with his own limited resources. If a regulatory framework grants certainty about funding and return on investment, the regulatory proximity is high.

Regulations at the macro level can be both a stimulating or constraining factor for innovation: *"[..]Too much institutional proximity is unfavourable for new ideas and innovations due to institutional lock-in (obstructing awareness of new possibilities) and inertia (impeding the required institutional readjustments). On the other hand, too little institutional proximity is detrimental to collective actions and innovation due to weak formal institutions[..]"*(Boschma 2005). The regulatory frameworks that are already in place when an emerging technology comes into being, are co-constructed around a (once emerging) technology that now has become a dominant design. The regulations are mutually dependent on each other, which results in *"complementarities"* (Hall and Soskice 2001). A change in one of the regulations in this *"local inertia"* (Boschma 2005) might lead to instability (Hannan and Freeman 1977). In order not to 'upset' the whole regulatory framework as a reaction to this possible instability, none or only very local regulatory changes may occur (Boschma 2005). At the same time, actors with vested interests (Herrigel 1993) in the existing technology and surrounding framework may react very conservatively to change towards the emerging technology (Grabher and Stark 1997) because change could undermine their position. New developments require a suitable regulatory framework and therefore older frameworks often need to be restructured, destructed, or new ones have to be constructed (Schumpeter 1934; Freeman and Perez 1988).

At the *meso level*, contracts between stakeholders in networks reduce uncertainty among the stakeholders within the network regarding Intellectual Property Rights (IPR) and unwanted spill-overs. Arrangements on patents, (co-)ownership and the licencing of these patents are made in contracts or mutual agreements between stakeholders. This reduces uncertainty regarding the ownership of the knowledge that results from the efforts of the stakeholders within the network. The contracts also prevent unwanted knowledge spill-overs to organisations outside the network. Which knowledge is allowed to 'leave' the network, and under which circumstances, is regulated in so-called Non Disclosure Agreements (NDA). NDAs can be important when scientific stakeholders want to publish findings in scientific articles, while industrial stakeholders first want to protect new ideas through patent applications[8]. Mutual agreements between stakeholders represent high regulatory proximity at the meso level.

#### *Cultural proximity*

The complexities of collaboration and the inherent uncertainty surrounding emerging technologies *"render it generally impossible to encode all contingencies in a contract, and, as a consequence, these networks have to rely at least partially on less formal institutions*

8 Once a new idea has been revealed in public (e.g. on a poster during a scientific conference), the idea can no longer be patented.

*that reduce the risk of opportunism*" (Ponds, Oort et al. 2007). Therefore, informal institutions or rules are important as well. *Cultural proximity* refers to the informal 'rules' between the stakeholders in the network. These informal rules encompass sets of routines and established practices (Edquist and Johnson 1997, p46), norms and habits (Boschma 2005), or ways of working (Tracey and Clark 2003). Scientific exploration and industrial exploitation (including R&D) take place in different structures (Dasgupta and David 1994). In science-industry collaborations cultural differences occur due to the fundamental difference between science and industry: *"the logic of scientific discovery does not adhere to the same logic that governs the development of new technologies"* (Gittelman and Kogut 2003). Science stakeholders primarily focus on knowledge creation and diffusion through scientific articles. On the other hand, industry stakeholders want to minimise the diffusion of knowledge through patents and focus on applications. Therefore, *"the world of science and the world of technology can be seen as two different communities with their own set of [informal] rules and behaviour"* (Ponds, Oort et al. 2007). The result is a difference in underlying incentive structures for science and industry (Dasgupta and David 1994; Frenken and Van Oort 2004). Stakeholders that are of the same organisational type have the same underlying incentive structure, which has a positive influence on interactive learning. In that case it can be said that cultural proximity is high.

***Social proximity***

Of specific interest for emerging technologies, where knowledge is often tacit, is the presence of trust. Trust refers to a relation of reliance between stakeholders. Stakeholders that trust each other are confident that they will act as agreed (e.g. not 'leaking' knowledge to parties outside the network). Since trust is embedded in social relations between stakeholders, this dimension of proximity is referred to as *social proximity.* Trust can be based on friendship, kinship or experience from earlier relations (Boschma 2005).

Trust is regarded as a capability that supports learning and innovation since it facilitates the exchange of tacit knowledge (Maskell and Malmberg 1999). In emerging technologies knowledge is often tacit (Arundel and Geuna 2004) or needs additional tacit explanation (Howells 2002). Tacit knowledge is transmitted more easily within relations in which the stakeholders trust each other. The ubiquitous character of tacit knowledge (i.e. available anywhere, anytime at marginal cost for every extra unit) in emerging technologies results in a very peculiar knowledge marketplace; the user of tacit knowledge wants to know what specific knowledge he is acquiring, whereas the producer does not want to give away too much knowledge of the definite transaction in advance. At the same time, stakeholders in networks in emerging technologies where knowledge from different fields has to be combined are mutually dependent on each other's knowledge. When combining their tacit and codified complex complementary knowledge, they have to trust that no one will misuse it for their sole benefit (Nahapiet and Ghoshal 1998), e.g. that one of the stakeholders will apply for a patent on the basis of complementary knowledge from other stakeholders within the network. If stakeholders trust each other, social proximity is high.

There might also be adverse effects of trust; it can lead to lock-in, preventing the influx of new stakeholders and knowledge into existing networks that are built on earlier (historical) relations. Also the risk of opportunism by other stakeholders

within social relations might be underestimated (Uzzi 1997). *"Often, active intervention is required from the part of the program's coordination and management function to facilitate the build-up of trust, reduce the threat of opportunism, and facilitate interaction between partners with complementary resources and needs."* (Autio, Kanninen et al. 2008)



### *Organisational proximity*

*Organisational proximity* relates to how stakeholders coordinate their actions in an *"organisational arrangement"* (Boschma 2005). These arrangements can range from a single (intra)organisational unit to a collaboration of stakeholders in networks. Within collaborations in emerging technologies, stakeholders create and combine new knowledge, and *"knowledge creation [..] depends on a capacity to coordinate the exchange of complementary pieces of knowledge owned by a variety of actors"* (Boschma 2005). Besides the coordination of knowledge exchange, innovation is also dependent on the autonomy of the individual stakeholders within the organisational arrangement. Individual stakeholders working on their own (i.e. autonomously) should be able to pursue their quest for knowledge, unhindered by too restrictive settings because unexpected insights and serendipity might lead to exploring new possibilities instead of following fixed (or even outdated) working packages and routines. Innovation is dependent on both the free flow of knowledge and the coordination of complementary knowledge search processes. Therefore, organisational proximity *"involves the rate of autonomy and the degree of control[9]"* (Boschma 2005), and there should be an optimum between these two prerequisites. According to Hansen (1999), in general, strong ties (i.e. close and frequent relationships) between the stakeholders stimulate the transfer of complex knowledge. However, too strong ties become counterproductive due to i) lock-in, ii) incomplete or fewer feedback loops in asymmetrical relations, and iii) hampering flexibility (Blanc and Sierra 1999). *"In loosely coupled networks where the identity and separateness of elements is preserved, the network can potentially retain a greater number of mutations and novel solutions than would be the case with a tightly coupled system"* (Grabher and Stark 1997). Therefore, when looking at networks of stakeholders that are combining their efforts in the development of an emerging technology we will look at the balance between autonomy and coordination (Boschma 2005).

### *In summary*

In this section we have focused on the conditions for interactive learning: *geographical, cognitive, regulatory, cultural, social* and *organisational* proximity. In the next section we look at the relation between the conditions for interactive learning and the interactive learning process.

9 Which Boschma also calls coordination (Boschma 2005).

## 2.5 Relations between the conditions for interactive learning and the interactive learning process

In the 'classical' proximity approach, a direct link is often assumed between proximity and the interactive learning outcome (and even innovative performance), and no distinction is made between the interactive learning process and the interactive learning outcome. In the Framework for Interactive Learning in Emerging Technologies we open the black box of interactive learning. Therefore, based on the description of the conditions for interactive learning and the elements of the interactive learning process, we can propose relations between the dimensions of proximity and the elements of the interactive learning process, i.e. *prime mover, network formation, intermediary*, and *knowledge flows*.

Relations between the conditions for interactive learning and the prime mover:

- *Geographical proximity* facilitates face-to-face interaction, which enables tacit and complex knowledge exchange. Stakeholders at an appropriate geographical distance are able to exchange tacit and complex knowledge better during the collaboration. Therefore, it is assumed that *geographical proximity* influences *the prime mover* in his search for complementary stakeholders; the prime mover is assumed to look for stakeholders in his close vicinity.
- A prime mover is driven by a sense of urgency and mutual dependency. The sense of urgency encompasses the problem perceived by the prime mover and the solutions that might be provided through the emerging technology. In order to arrive at these solutions the prime mover is dependent on complementary knowledge and resources of other stakeholders. The prime mover's knowledge pool needs to be complemented with knowledge from other stakeholders. Therefore, based on the prime mover's cognitive strengths and weaknesses, it is assumed that a prime mover will look for stakeholders who can contribute necessary complementary knowledge and who are able to absorb each other's complementarities. As such, *cognitive proximity* influences the actions of the *prime mover.*
- It is also assumed that the *prime mover's* first steps in building a network to further develop the emerging technology are influenced by *regulatory proximity* at the macro level[10]. Regulations, that for example create a protected market space for the emerging technology, offer some security for return on investments. This reduces uncertainty and stimulates the prime mover to undertake action on new, uncertain, emerging technological fields. Also the availability of government funding might stimulate the prime mover to venture into risky, long-term and costly research.
- Since differences in *culture* (i.e. different underlying incentive structures) between the stakeholders might influence the collaboration, it is assumed that the *prime mover* will (first) contact stakeholders with the same underlying incentive structures. Organisations operating under the same underlying incentive structure have the same focus, which is expected to prevent conflicting situations (e.g. publicising or patenting).

10 The influence of regulations at the meso level on the interactive learning process is related to the knowledge flows. This relation is discussed later.

- Trust is important for the exchange of tacit knowledge between stakeholders and therefore *social proximity* between the prime mover and the stakeholders and among the stakeholders themselves is assumed to influence the prime mover when looking for complementary stakeholders. If there is insufficient trust between the stakeholders, the exchange of (tacit) knowledge during the collaboration will be hampered. Trust is based on earlier experience and/or collaborations.

Relations between the conditions for interactive learning and network formation:

- Tacit and complex knowledge is not only interchanged during the actual scientific research, but also during network formation (e.g. during the co-construction of a shared vision). Therefore it is assumed that *geographical proximity* influences *network formation* since it facilitates face-to-face interactions in which tacit and complex knowledge can be interchanged.
- A network of heterogeneous stakeholders will only be formed if the involved stakeholders are able to learn from each other. It is assumed that *cognitive proximity* influences *network formation* because both a cognitive distance between the stakeholders (creating a potential for learning), as well as a certain amount of absorptive capacity to bridge the potential knowledge gap has to be present.
- *Regulatory proximity* at the macro level reduces uncertainty about return on investment and can generate research funding. This stimulates stakeholders to cooperate in risk bearing, costly long-term projects and to form networks. Often government funding requires cooperation between various stakeholders, thereby stimulating network formation. Therefore, it is assumed that *regulations* at the macro level that reduce uncertainty and provide funding influence *network formation* of stakeholders that embark on risky, costly research.
- For interactive learning, stakeholders have to combine their complementary knowledge. While the stakeholders are collaborating within the network, outside the network, the stakeholders might operate under different incentive structures, or might even be rivals. Therefore it is assumed that a difference in *culture* might negatively influence the network formation of heterogeneous stakeholders because it is expected that a difference in underlying incentive structure might hamper knowledge exchange during research due to opposing interests (i.e. early publishing versus secrecy for patenting).
- For interactive learning in emerging technologies, stakeholders must trust each other that their knowledge will not be misused. As such, it is assumed that *social proximity* (i.e. trust) influences *network formation*: if stakeholders trust one other they will consider forming a network for cooperation.

Relations between the conditions for interactive learning and the intermediary:

- If there is a cognitive distance between the stakeholders that cannot be bridged due to a lack of absorptive capacity, an intermediary might act as a translator between these stakeholders. Geographical proximity enables face-to-face interactions that facilitate the exchange of tacit and complex knowledge. Therefore it is assumed that *geographical proximity* influences the *intermediary* because close geographical proximity of the intermediary enables the intermediary to translate tacit and complex knowledge between the stakeholders.

- The cognitive distance between the other stakeholders for which the intermediary is acting as a translator also influences the *intermediary*. If there is very little cognitive distance between the stakeholders, an intermediary is superfluous. By the same token, when the cognitive distance between the stakeholders is too large, even an intermediary might not be able to bridge the knowledge gap between them. It might be expected that the intermediary is at a cognitive distance between the involved stakeholders for translating knowledge between these stakeholders and helps them to bridge knowledge gaps.

Relations between the conditions for interactive learning and knowledge flows:

- Since *geographical proximity* facilitates face-to-face interaction, which enables the exchange of tacit and complex knowledge, it is assumed that geographical proximity influences *knowledge* flows between stakeholders.
- Cognitive distance is a prerequisite for interactive learning in science-based emerging technologies in which complementary complex knowledge from heterogeneous stakeholders has to be combined in order to innovate. Therefore, it is assumed that the *cognitive distance* between the heterogeneous stakeholders has an influence on *knowledge flows* in the interactive learning process. The greater the distance between the knowledge pools of the stakeholders, the more knowledge has to be exchanged.
- It is assumed that *regulatory proximity* at the meso level influences *knowledge flows* because mutual agreements reduce IPR uncertainties and unwanted spill-overs, which otherwise might hinder the free flow of knowledge between stakeholders.
- *Cultural proximity* is related to different underlying incentive structures for science and industry, which might induce reluctance to knowledge sharing and could block knowledge flows and interactive learning. As a result, it is assumed that *cultural proximity* influences *knowledge flows*.
- Stakeholders have to trust each other that they will not misuse complementary knowledge for their sole benefit (e.g. publicising or patenting), otherwise knowledge flows might be hindered. Consequently, it is assumed that *social proximity* influences *knowledge flows*.
- Flexibility enables individual stakeholders to pursue their own knowledge goals, whereas coordination enables the combination of complementary knowledge flows. Therefore, it is assumed that *organisational proximity* influences the 'production' of *knowledge* in flexible settings (e.g. research projects with a high degree of freedom (and serendipity), and the combination of complementary knowledge resulting from research projects through coordination.

***In summary***

Based on the proximity concept we identified six conditions that influence the interactive learning process in emerging technologies: geographical, cognitive, regulatory, cultural, social and organisational proximity. From the identification and analysis of these conditions and the suggested relations with the interactive learning process we can complement the Framework for Interactive Learning in Emerging Technologies (Figure 7).

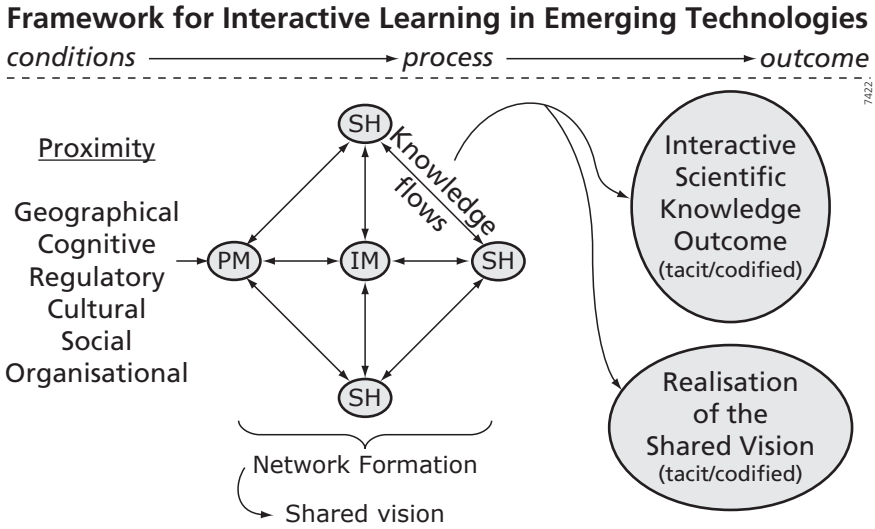


**Figure 7** The developed Framework for Interactive Learning in Emerging Technologies (PM=prime mover; IM=intermediary; SH=other stakeholders in network)

## 2.6 Conclusion

In this chapter we developed a Framework for Interactive Learning in Emerging Technologies. Contrary to earlier work on learning, we did not only look at the outcome of the interactive learning process, but also started to open the black box of interactive learning. We started out from the importance of interactive learning in emerging technologies for the exchange of tacit and complex knowledge and the realisation of a shared vision that acts as a driver for innovation. From this starting point we developed a framework based on elements of the interactive learning process (i.e. prime mover, network formation, intermediary and knowledge flows), influencing conditions (geographical, cognitive, regulatory, cultural, social and organisational proximity) and the outcome of the interactive learning process (interactive scientific knowledge outcome and realisation of a shared vision; both tacit and codified).

In Chapter 4 we present the methodology that allows us to explore the developed FILET. Through the exploration in case studies (Chapters 5 and 6) we can study whether the elements of the FILET constitute a usefull and complete framework, and whether the assumed relations between the elements constitute a correct conceptualisation of interactive learning. Based on the exploration of the FILET we are able to draw conclusions at the aggregate level and assess the validity of the FILET (Chapter 7). But first we take a closer look at the emerging technology of nutrigenomics in the next chapter.

# 3 Nutrigenomics, an emerging technology

In the previous chapter we developed the Framework for Interactive Learning in Emerging Technologies (FILET). For an initial exploration of the FILET we apply the framework in the emerging technology of nutrigenomics. In this chapter we answer the *sub-questions*:

4. *What is nutrigenomics and what are the expectations surrounding nutrigenomics?*
5. *Is the emerging technology of nutrigenomics a hot spot?*



In this chapter we first present a short history of nutrition research (§3.1). We then move on to elaborate on the characteristics that define nutrigenomics as an emerging technology: emerging technologies are characterised by the absence of a dominant design or definition and (hardly) any commercially available applications (Utterback 1994) (§3.2). An emerging technology is surrounded by uncertainties and open ends about future applications and related expectations (Nelson and Winter 1977) (§3.3). But within an emerging technology there is a visible increase of linkages between stakeholders (i.e. network formation) (Van Merkerk and Van Lente 2005) (§3.4). Additionally, we perform a scientometric analysis in order so assess whether or not nutrigenomics is a so-called *hot spot* and if interactive learning occurs within the nutrigenomics. In emerging technologies that attract the attention of industry and science – expressed in number of (co-) patents and (co-) publications -interactions between stakeholders are becoming visible and knowledge is being created (§3.5). Finally we draw conclusions in §3.6.

## 3.1 A short history of nutrition science

As far back as 400 BC the Greek philosopher Hippocrates stated *"let food be your medicine"*. According to Schneider (1977) since then three phases can be distinguished in nutrition science: the first phase started with Hippocrates and lasted 2000 years until the middle of the 18$^{th}$ century. In this era the simple presupposition was that foods contained 'nutriment' and the only difference between various foods was their quantity of 'nutriment'. The founding of chemistry as a scientific field in the middle of the 19$^{th}$ century launched the second phase in nutrition science. Through the chemical analyses of foodstuffs it became evident that food contained more than one 'nutriment'; a distinction could be made between minerals, fats, proteins and carbohydrates. Around the beginning of the 20$^{th}$ century, the third era started when a biological approach instead of a chemical approach was taken towards food. In this era animal studies arose and 'new' food ingredients were discovered; micronutrients like vitamins and trace minerals.


**Figure 8** The cover of Science in which the first results of the Human Genome Project were presented (www.sciencemag.org 8-12-2008)

We can distinguish a fourth phase since the beginning of the second millennium: the genomics revolution (Quirk 2003; Wilkinson and Targonski 2003). In 2001, the first results of the world wide Human Genome project, initially headed by Watson[11], were simultaneously presented in Nature (The International Human Genome Mapping Consortium 2001) and Science (The Celera Genomics Sequencing Team 2001) (Figure 8). The project identified the approximately 20,000 – 25,000 genes of the human genome. *"The[se] genomics developments have changed research drastically. New technology has become available, studying pathology has become much easier, and the research approach has changed; nowadays you have 'donors within the PC' with 'whom' you can do various experiments as fast as lightning"* (interview 2006-07-04). The identification of the human genome opened up possibilities to study the relation between the genome, nutrition and health; this is called *nutrigenomics*.

## 3.2 Defining nutrigenomics

According to nutrigenomics scientists, nutrigenomics is an emerging technology (Fogg-Johnson and Kaput 2003; Mutch, Wahli et al. 2005; Kaput, Perlina et al. 2007). Nutrigenomics appears to be a 21st century term as the word was not used before then (Ghosh, Skinner et al. 2007). Other terms in use are 'nutritional genomics', 'nutriomics' (Arab 2004), and also 'nutritional genetics' and 'nutrigenetics'. Formally, there is a difference between nutri*genomics* and nutri*genetics*, but both terms are often used in the same publication (Levesque, Ozdemir et al. 2008). Nutri*genomics* is *"the study of the genome-wide influences of nutrition or dietary components on the transcriptome, proteome and metabolome, of cells, tissues or organisms, at a given time"*. Nutri*genetics* is *"the relationship between genotype and the risk of developing diet-related diseases, such as cancer, diabetes type II and cardio-vascular diseases"* (Müller and Kersten 2003).

11 Together with Francis Crick, James Watson discovered the DNA double helix structure.

In other words, nutri*genomics* looks at the influence of nutrition on the genome and nutri*genetics* at the risk of nutrition-related diseases. Despite this formal difference in definition, the terms nutri*genomics* and nutri*genetics* are used interchangeably for the designation of research that contains nutri*genomics* and/or nutri*genetics* elements in order to gain insight into the genome, nutrition and disease risks. Illustrative for the overlap between nutrigenomics and nutrigenetics is the Journal of Nutrigenetics and Nutrigenomics of the International Society on Nutrigenetics/Nutrigenomics (ISNN)[12]. On the Internet, the term nutrigenomics is used four times more than nutrigenetics[13]. Throughout this book we use the term nutrigenomics.

The word 'nutrigenomics' is a contraction of 'nutrition' and 'genomics'. As such, the word nutrigenomics indicates the complementarities and mutual dependency between the knowledge fields of nutrition and genomics. The goal of nutrigenomics research is to gain insight into the relation between the genome, nutrition, and diet-related diseases (Müller and Kersten 2003). The relation between genes, nutrition and diseases can be described in five steps (Kaput 2004):

1. Common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure;
2. Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases;
3. Some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases;
4. The degree to which diet influences the balance between health and disease may depend on an individual's genetic make-up; and
5. Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype (i.e. individualised nutrition) can be used to prevent, mitigate, or cure chronic disease.

The tool box for nutrigenomics research contains four *"complementary technolog[ies]"* (Van der Werf, Schuren et al. 2001): *Genomics* is a method for the sequencing of whole genomes. For example, the human genome has been sequenced in the Human Genome Project. In order to study the activity of the genome in response to different conditions, *transcriptomics* is used to study the presence of mRNA[14] as an indicator for gene expression. In order to obtain detailed insight into cellular functions the proteome content of cells has to be studied through *proteomics*. *Metabolomics* allows the study of the presence of metabolites[15] in cells under different conditions. The resulting insights can be used as biomarkers that can function as starting points for disease prevention. The 'merge' of these 'omics' technologies creates new possibilities for nutrition research:

12 (content.karger.com/ProdukteDB/produkte.asp?Aktion=JournalHome&ProduktNr=232009 16-11-2008)

13 221,000 hits for nutrigenomics and 51,200 for nutrigenetics on www.google.com (16-11-2008)

14 I.e. the transcriptome.

15 I.e. metabolism intermediates, very small molecules.

*"The interaction between the human body and nutrition is an extremely complex process involving multi-organ physiology with molecular mechanisms on all levels of regulation (genes, gene expression, proteins, metabolites). Only with the recent technology push have nutritional scientists been able to address this complexity. Both the challenges and promises that are offered by the merge of 'biomics' technologies and mechanistic nutrition research are huge, but will eventually evolve in a new nutrition research concept: nutritional systems biology [i.e. nutrigenomics]."* (Corthésy-Theulaz, Dunnen et al. 2005)

Figure 9 gives a graphical representation of the relations between nutrition, the genome and disease, and the four above-mentioned complementary technologies (Van der Werf, Schuren et al. 2001) according to Müller and Kersten (2003).

A simplified image for nutrigenomics is sketched by Penders (2008) (Figure 10). Nutrigenomics research focuses on the influence of nutrition on the genome and health. His simplified nutrigenomics image presents a good overview of this nutrigenomics research. However, within nutrigenomics research numerous complicating factors are at play. First, nutrition does not have a uniform composition; the apple you eat today can have another composition and amount of nutrients than tomorrow's apple. Therefore, there is no uniform daily dose. Second, diseases are seldom caused by only one gene. Often multiple genes are at work. Third, different genotypes might result in the same disease (Kaput, 2008). Fourth, genes also influence each other (i.e. epistasis); the expression of one gene might lead to the expression or inhibition of another gene,

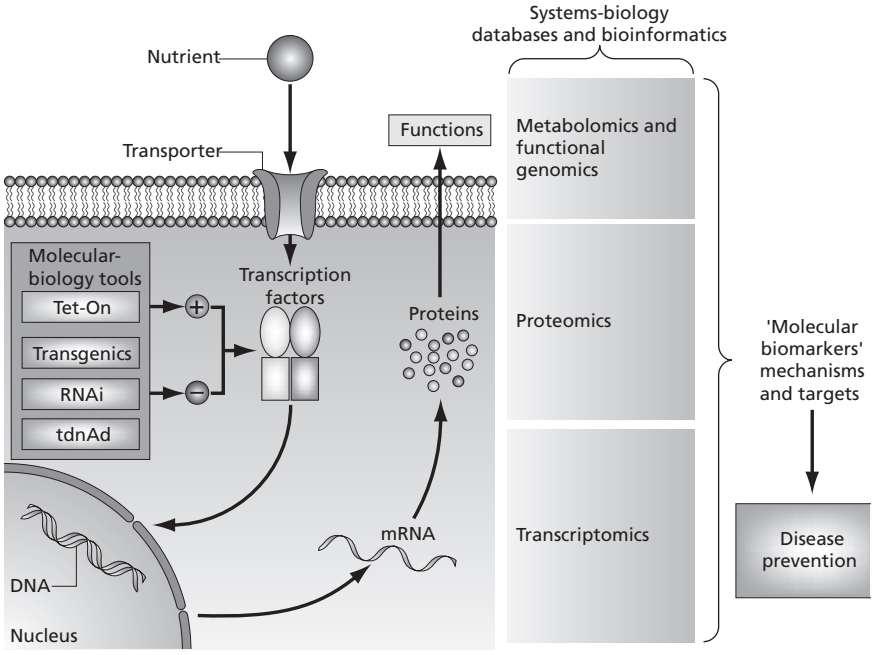


**Figure 9** Nutrigenomics, the relation between nutrition, the genome and diseases as depicted by Müller and Kersten (2003).

causing or preventing disease. Fifth, besides these mechanisms there are also structural variations in the human genome of individuals. Sixth, these differences are not only related to different genomes, but also to epigenetic effects. Epigenetics is the change in phenotype or gene expression not related to a change in DNA sequence. Consequently, *"[d]eveloping individual risk factors in light of the genetic diversity of human populations, the complexity of foods, culture and lifestyle, and the variety of metabolic processes that lead to health or disease is a significant challenge for personalising dietary advice for healthy or individuals with chronic disease "*(Kaput 2008).

We have shown that different words are used for nutrigenomics (Arab 2004), that nutrigenomics and nutrigenetics are used interchangeably (while there is a technical difference) and we have explained the general principle underlying nutrigenomics (Müller and Kersten 2003; Kaput 2004). For the time being there is no dominant definition in use for nutrigenomics. Experts have different opinions about the genome that should be studied. Some nutrigenomics scientists state that only the human genome is the subject of study. Other scientists also mention the study of the food genome, or of both the human and the food genome (Ronteltap, van Trijp et al. 2007). In our interviews with nutrigenomics stakeholders we also encountered different definitions or interpretations of nutrigenomics, for example:

*"Through my eyes, nutrigenomics is to understand the hereditary qualities of the cow and how these influence the end product"* (interview 2006-09-29).

*"The influence of food components on various processes in our body on gen level. [..] From this knowledge we can get a better understanding of metabolic processes in our body and by that a better understanding of mechanisms behind the relation food-health.*

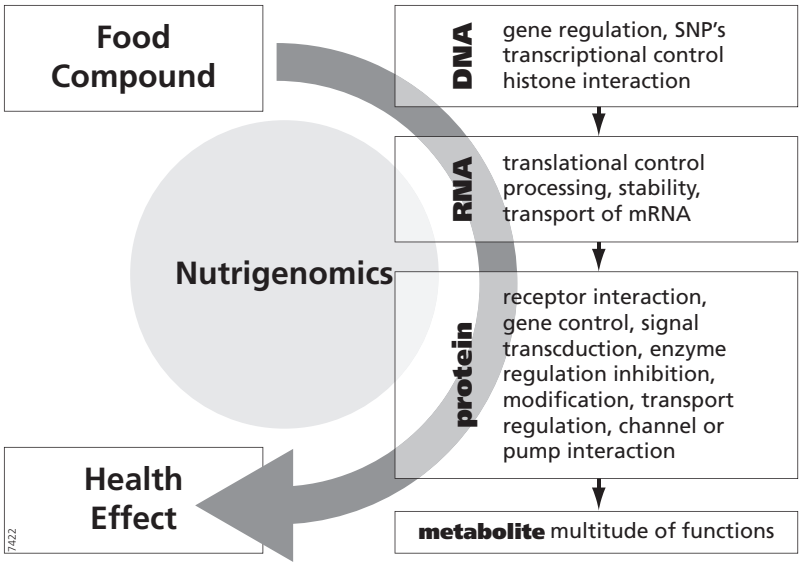


**Figure 10** 'Simplified Nutrigenomics' (Penders 2008) based on (van Ommen 2004)

*But also to arrive at new measurement methods and biomarkers to establish better what the effect of food on metabolic processes is on our body on the short term, but also related to the long-term.*" (interview 2006-07-10)

Between the experts in the Ronteltap study there was also discussion whether future applications should be incorporated into the definition (Ronteltap, van Trijp et al. 2007). For our research we will use the term nutrigenomics for all research into the relationship between genomes, nutrition and disease (risk) and the future applications that might result from that research.

## 3.3 Nutrigenomics innovations and expectations

For the time being there are no commercially available nutrigenomics products. Nevertheless, there are high expectations for nutrigenomics in terms of future product, process and service innovations and their potential contribution to disease prevention and health care. *"Nutrigenomics will first emerge as a process innovation, then as a service innovation and only then as a product innovation"* (interview 2006-08-18). The expected nutrigenomics product innovations are functional foods. Process innovations are related to the health claims of these functional foods that can be substantiated through nutrigenomics research processes. Service innovations encompass nutrigenomics tests that indicate disease risk factors. These innovations might contribute to the prevention and treatment of nutrition-related genetically predisposed diseases like the Metabolic Syndrome. Thus, there are three possible applications for nutrigenomics that can all contribute to the prevention and treatment of diseases like the Metabolic Syndrome.

First, the most concrete application of nutrigenomics is the development of functional foods. A functional food is a food product that has *"the potential to reduce the risk of lifestyle related diseases"* (Arai, Yasuoka et al. 2008). Since the 1970s, Yakult is a well known example of a functional food with a health claim. *"Drinking at least one bottle (65 ml) of Yakult per day may 1) improve bowel habit in subjects who are susceptible to constipation and 2) may support a well-balanced gut microbiota through an increased number of lactobacilli"* (Voedingscentrum 2006). With the aid of nutrigenomics research, functional foods could be designed that prevent disease and promote health (Gaisser 18 April 2008).

The functional food market is very interesting for food companies because; 'eating healthy' is becoming more and more popular (Mellentin 2005), which creates market opportunities for healthy products like functional foods. The total world food market is stable at € 3800 billion (Innovatienetwerk 2006). While in the years 2004 and 2005 the overall turnover of A-branded food products decreased, health-related products (such as Becel pro-activ and Yakult) showed an increase (Ministerie van Economische Zaken 2006). It was estimated in 2004 that worldwide $44 billion ($11 billion of which in Europe) turnover was generated by functional foods. Between 1998 and 2003 the functional food market grew by 60% (Euromonitor 2004). It is expected that growth of the world market for functional foods will increase up to 2010. By that time the world market share of functional foods will be approximately 5% (Just-Food.com 2004).

**Table 2** Functional foods with a scientifically tested hard claim in the Netherlands and their effects on human health (www.voedingscentrum.nl/EtenEnGezondheid/Toevoegingen/functionele+voeding/aanbod.htm 18-11-2008)

| Product | Scientifically-proven hard claim | Required quantity |
|---|---|---|
| Benecol margarine with added fytostanols | Helps reduce cholesterol level in the blood (approximately 10%) | Daily 2-3 sandwiches with spread |
| Becel pro.activ margarine with added fytosterolesters | Helps reduce cholesterol level in the blood (approximately 10%) | 3 portions daily |
| Vitaal bread with added prebioticum (inuline) | Supports the bowel function | 3 slices daily |
| Danone Activia Yoghurt with added probiotica (bifidobacteria) | Stimulates the stool, if delayed | At least one portion daily |
| O'mega bread with fish acids | Reduces the risk of coronary heart diseases like heart failure en heart infarcts | Regular consumption |
| Vitaal bread Pró-FIT with béta-glucan | Helps reduce cholesterol level in blood (approximately 3%) | 4 slices daily |
| Vifit | Supports barrier function of the colon | One portion daily |
| Yakult | Can improve the stool, contributes to well-balanced bowel flora, | One portion or more daily |
| Halvarine and yoghurt from Albert Heijn with Reducol (fytosterols and -stanols) | Reduces cholesterol in blood (up to 10%) | 3 portions halvarine or 1 yogurt |
| OatWell® (=Cereacol®) cereal product | Decrease in LDL cholesterol by 4-6% | 1-4 portions daily |

Second, the application of nutrigenomics research itself is a process innovation. This process innovation is closely related to the nutrigenomics product innovations in the form of functional foods. In functional foods a distinction is made between *hard* claims and *soft* claims about the health effects of a functional food. *Hard claimed* functional foods have a scientific evidence base for the relation between the functional food and health. *Soft claims* only suggest a positive contribution of the functional food to health. Table 2 presents an overview of hard claimed functional foods available on the Dutch market; only a minority of available functional foods is supported by a hard claim. The insight into genomics-nutrition interactions through nutrigenomics research might provide scientific evidence for the efficacy of functional foods. This becomes of importance because new legislation will only allow hard claimed functional foods on the market (EU Regulation 1924/2006[16]).

16 NB The proposal for this EU regulation was made in 2003 and was at that time known as (COM (2003) 424) (see http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:EN:PDF). At the time of the case studies the proposal still had to be ratified by all EU Member States.

Third, nutrigenomics can be applied as a service innovation in the form of 'nutrigenomics' tests. Technically speaking, these tests are nutrigenetics tests because they identify genetically predisposed risks. Personalised nutrition and lifestyle guidance can be given on the basis of the identified risk factors for disease. This advice might incorporate a personalised healthy diet and exercise programmes. The diet might also comprise functional foods.

Easy to use do-it-yourself nutrigenetics tests can already be ordered over the internet. An example of an internet-based company providing genetic test kits is 23andMe (Figure 11). Using 23andMe's genetic test kit is very easy: First a test kit is ordered over the internet. Second, saliva – which contains DNA – is collected and sent to 23andMe. Third, the saliva sample is analysed. Fourth, you can access your genome and risk profile online. One of the conditions 23andMe analyses is Diabetes Type-2 (www.23andme.com/health/type2diabetes 8-12-2008), one of the risk factors of the Metabolic Syndrome. On the basis of the analysis provided by 23andMe life style adjustments can be made that help to prevent disease risks like Diabetes Type-2.

In 2006, the United States Government Accountability Office evaluated four randomly chosen nutrigenetics tests that were available for consumers[17]. The study concluded that the evaluated tests *"mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers"* (United States Government Accountability Office 2006). Or, as an interview stated: *"Products offered by companies like Sciona deceive the public[18]"* (interview 2006-08-18).

Although there are high expectations for the application of nutrigenomics, as shown above, it will probably take some time before these expectations are realised: "*Nutrigenomics is a potential goldmine for the discovery of genes that are important as dietary targets [..] Although we think that the contribution of nutrigenomics to public health will be minor during the next five years, we believe that in the long-term, the field has the potential to make an important contribution.*" (Müller and Kersten 2003). When experts were asked about the future applications of nutrigenomics they did not foresee the first applications becoming commercially available on the market before 2010. Until then, the focus is on nutrigenomics research that provides insights into genome-nutrition interactions and disease that can be used for applications (Ronteltap, van

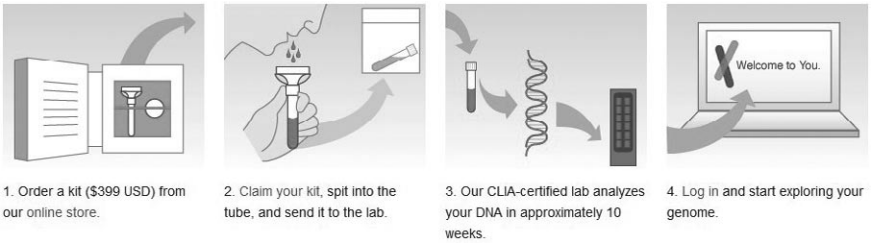


**Figure 11** The 23andMe genetic test procedure (www.23andme.com/health/type2diabetes 8-12-2008)

17 NB The GOA evaluation was performed before the launch of 23andMe.

18 "Volksverlakkerij" in Dutch.

Trijp et al. 2007) (Figure 12). Our own interviews with nutrigenomics stakeholders provided a similar overview, as for example was indicated in the statement in interview 2006-05-10: *"[In 5-10 years] we have increased our understanding regarding molecular effects of nutrition. This is very important for the food industry because it can help them with "evidence based" nutrition [..] which can help to make hard claims and perhaps to develop new effective foods quicker. [..] I'm confident that we can expect products that help people to live a healthy life."* Accordingly, more nutrigenomics research is first needed before applications might become reality.

The overall idea is that nutrigenomics research results in applications for personal nutrition and health care. On the basis of a nutrigenomics test and dietary advice consumers can purchase functional foods that have a health-promoting and disease-preventing benefit attuned to their genome and disease risk. One nutrition-related



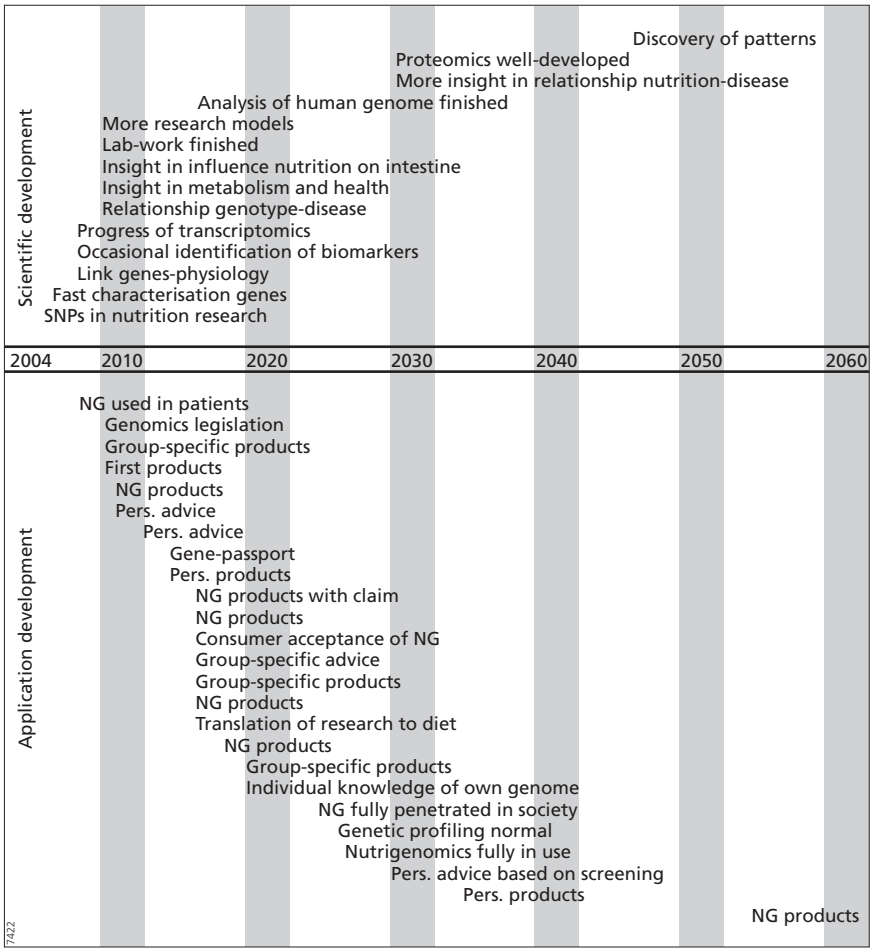


**Figure 12** Nutrigenomics development according to experts: first focus on research, from 2010 onwards first applications (Pers. = personalised; NG = nutrigenomics) (Ronteltap, van Trijp et al. 2007)

genetically predisposed disease is the Metabolic Syndrome. The Metabolic Syndrome[19] is a combination of risk factors that can eventually lead to cardio-vascular disease (Kahn, Buse et al. 2005). Risk factors that are generally accepted as being part of the Metabolic Syndrome are abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance with or without glucose intolerance, prothrombotic state, and proinflammatory state (www.health.gov/DIETARYGUIDELINES/dga2005/report/HTML/G1_Glossary.htm 17-11-2008). One of the major risk factors is obesity which, according to the WHO, *"is one of the greatest public health challenges of the 21st century. [..] Obesity is already responsible for 2-8% of health costs and 10-13% of deaths in different parts of [Europe]"* (www.euro.who.int 2008). The problem of obesity in the industrialised and industrialising world is so huge that the WHO has also called it *globesity* (www.who.int/nutrition/topics/obesity/en/index.html 17-11-2008).

There is some discussion about the Metabolic Syndrome. Different organisations proposed different definitions and diagnoses for the Metabolic Syndrome (Figure 13). In addition, issues have been raised as to whether or not the Metabolic Syndrome is in fact a syndrome, meaning that the sum of the diseases that constitute the Metabolic Syndrome is more than the co-existence of the individual diseases (Kahn, Buse et al. 2005). For example, general practitioners (GPs) in the Netherlands are aware of the Metabolic Syndrome. Nevertheless, the Metabolic Syndrome is not incorporated in the NHG standards[20]; the risk factors and diseases that are part of the Metabolic Syndrome are treated separately (interview 2008-11-18). Risk factors and diseases are treated separately because of a lack of scientific evidence[21]. Many (scientific) questions have to be answered in order to obtain a clear understanding of nutrition-related, genetically predisposed diseases like the Metabolic Syndrome. The Center for Disease Control's (CDC) National Office of Public Health Genomics provides an overview of the well-knowns and unknowns in the relationship between genetics and obesity, one of the major risk factors for the Metabolic Syndrome. This overview shows that many questions still have to be answered. Some of these questions are (www.cdc.gov/genomics/training/perspectives/files/obesknow.htm 28-11-2008):

- How do genetic variations that are shared by obese people affect gene expression and function?
- How do genetic variation and environmental factors interact to produce obesity?
- What are the biological features associated with the tendency to gain weight?
- What environmental factors are helpful in countering these tendencies?

---

19 Synonyms used for the Metabolic Syndrome on internet and throughout (scientific) publications are metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome, and CHAOS.

20 The NHG standards contain guidelines for diagnosis and treatment. The standards are not only used by general practitioners (GPs) in the Netherlands, but have also been adopted by GPs in Europe because of the evidence-based medicine in the Netherlands (interview 20081118)

21 Note 6 in the NHG-standard for Diabetes Mellitus Type-2 refers to the Insulin resistance syndrome and that – for the time being – there is no clearness of the meaning of the involved risk factors in daily practice. (nhg.artsennet.nl/upload/104/standaarden/M01/std.htm#noot6 noot6, 18-11-2008 #848)

**Table 1—*Definitions of the metabolic syndrome***

| |
|---|
| ATP III definition (27,28) |
| Any three or more of the following criteria: |
| *1)* Waist circumference >102 cm in men and >88 cm in women |
| *2)* Serum triglycerides ≥1.7 mmol/l |
| *3)* Blood pressure ≥130/85 mmHg |
| *4)* HDL cholesterol <1.0 mmol/l in men and <1.3 mmol/l in women |
| *5)* Serum glucose ≥6.1 mmol/l (≥5.6 mmol/l may be applicable) |
| WHO definition (26) |
| Diabetes, IFG, IGT, or insulin resistance (assessed by clamp studies) and at least two of the following criteria: |
| *1)* Waist-to-hip ratio >0.90 in men or >0.85 in women |
| *2)* Serum triglycerides ≥1.7 mmol/l or HDL cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women |
| *3)* Blood pressure ≥140/90 mmHg |
| *4)* Urinary albumin excretion rate >20 μg/min or albumin-to-creatinine ratio ≥30 mg/g |

**Figure 13** Two definitions of the Metabolic Syndrome (Kahn, Buse et al. 2005)

The discussions surrounding the Metabolic Syndrome leave unimpeded the efforts made within the emerging technology of nutrigenomics to gain insight into the complex relationships between genome, nutrition and diseases in order to find new prevention and treatment strategies for nutrition-related genetically predisposed diseases. In our research we are interested in the interactive learning between the stakeholders involved in this complex nutrigenomics research.

## 3.4 Nutrigenomics stakeholders

As we saw above (§3.2), nutrigenomics is the study of the relationship between nutrition, the genome and disease, for which four complementary 'omics' technologies and numerous research techniques are employed (Van der Werf, Schuren et al. 2001). Therefore, scientific stakeholders with knowledge on nutrition, genomics, and specific research techniques are performing nutrigenomics research. This might result in future applications like functional foods and nutrigenomics tests (§3.3). Consequently, companies are triggered by the future applications that might result from nutrigenomics research. One way for companies to become involved in this research is though collaboration or the acquisition of nutrigenomics related (smaller/start-up) companies: DSM participated in *"personalised nutrition company Sciona"* (interview 20070516) (DSM 2006) and Roche Vitamins (interview 2006-06-28) and

Unilever invested in Perlegen, with expertise in human genetic variability (interview 2006-05-03).

The emerging technology of nutrigenomics not only attracts the attention of research organisations and companies, but also the attention of patient and consumer organisations that might benefit from the scientific insights and applications. Patient and consumer organisations not only raise issues regarding nutrigenomics and inform their members about future possibilities (e.g. cures and treatments), but also actively participate in the exploration of future applications. For example, the patient organisations European Genetic Alliances' Network (EGAN), the International Genetic Alliance (IGA) and DSM Food Specialties formed an alliance for preventive health management in which the role of nutrition and genomics are explored (DSM 2006) (interviews 2007-02-23 and 2007-05-30).

As described in §3.3, at this moment scientific discoveries and breakthroughs in nutrigenomics research still have to be made before applications might become reality. For this research complementary knowledge from genomics, nutrition and disease is combined together with the expertise on specific research techniques required to perform this research. In their article, Van der Werf, Schuren et al. (2001) already mentioned 20 specific techniques involved in nutrigenomics research. Nutrigenomics research and the involved techniques also require major investments that seldom can be raised by a single stakeholder. It is impossible for a single stakeholder to cover all knowledge fields (i.e. nutrition, genomics and disease), to be familiar with all necessary research techniques, and to have the disposal of sufficient resources. This creates a mutual dependency between the stakeholders in nutrigenomics research. The expectations of scientific developments in nutrigenomics and the mutual dependency between stakeholders has stimulated the formation of various nutrigenomics consortia, in which research institutes and companies combine their knowledge, expertise and resources (Kaput, Ordovas et al. 2005). The Programme Director of the Dutch Top Institute Food and Nutrition (TFIN) explains the collaboration in nutrigenomics consortia as follows:

*"Rapid turnover of new products and at the same time a growing need for stronger substantiation for nutritional claims on food products drive the need for science and technology innovation in the food industry. The organisational flexibility and required funding exceed the possibilities of individual companies. Therefore, companies increasingly participate in networks that connect the fundamental science in academia with applied research and development executed within these companies. The structuring of these networks is a critical success factor for the contribution to the science and technology innovation power of the participating companies."* (TFIN 2008)

It is mainly in these consortia where interactive learning between stakeholders in nutrigenomics occurs. Table 5 in Chapter 4 presents an overview of the eight known nutrigenomics consortia worldwide.

To conclude, nutrigenomics has attracted the attention of research, industry, patient and consumer organisations. Since nutrigenomics is currently primarily science based, most stakeholder interactions and interactive learning is perceptible in nutrigenomics

consortia consisting of research institutes and companies. Therefore, we will focus in our study on these nutrigenomics consortia.

## 3.5 Scientometric analysis of nutrigenomics[22]

In order to obtain an overview of nutrigenomics developments we employed a scientometric analysis in order to assess whether or not the emerging technology of nutrigenomics is a so-called *hot spot* (Rothman 1997). A hot spot is a technology that draws relatively more attention from science and industry – expressed in publications and patents – compared to other technologies. The 'attention' of industry and science in emerging technologies implies research activities that are initiated in connection with the emerging technology, which leads to the creation and accumulation of knowledge. If this knowledge creation is related to interactive learning, this is perceptible in the presence co-publications and co-patents. In that case, the emerging technology becomes an interesting setting for the exploration of the FILET. Insight into patenting and publication over time also gives an overview of a technology's development.



### 3.5.1 Scientometrics data and methods

When mapping an emerging technology field some authors use the term *hot spot analysis* (Rothman 1997). In general, a hot spot stands out in its surroundings; it is 'hotter' and 'brighter': it concerns subfields that attract more attention within or across research communities than others, or countries that outperform other countries on the same subject. Such awareness can usually be measured by publication citation analysis. Unfortunately, citation analysis is not a suitable tool to capture awareness of emerging technologies as the number of citations of these technologies is generally assumed to be very low. This is because citations are influenced by a patent's or publication's age, which is very young in an emerging technology. To measure the latent concept of awareness we assume that indicators based on patents and publications serve as proxies. Patent data especially show the areas in which companies find it worthwhile to invest in and therefore patent data indicate what might become available on the market in the near future. Patent data are used because patents protect investments in R&D activities that businesses find worthwhile to pursue. Therefore, patent data are indicators of developments in a specific field.

The reason for using publication data is that scientists are always looking for new developments. They publish (i.e. codify) their scientific work in articles. Through the scientometric analyses of these articles we can develop a better understanding of new knowledge fields and the increase in attention scientists pay to these fields. Therefore, articles are an indicator of scientific activity in a specific field. The relative growth of patents and publications in a specific R&D subfield or technology compared to other subfields (or a R&D field in one particular country compared to other countries) indicates hot spots.

The advantages and disadvantages of using patent and publication data as indicators of innovation are well-known and have been discussed at length by several

22 This section will be published as: Vandeberg, R. L. J. and W. Boon (2009). *"Identifying Innovation Hot Spots in Genomics."* Genomics, Society and Policy.

authors (Kleinknecht, Van Montfort et al. 2002): Advantages of using patents include the availability of historical time series, detailed classification by technological subfield, and easy access. Disadvantages include: differences in propensity to patents across countries, sectors and even over time, a disregard for other types of knowledge that cannot be patented or are not patented because of strategic reasons, differences in patent procedures across countries, and the inability to diversify between patents that are economically valuable and those that are not. A disadvantage of publications is the time that lies between discovery and publication. Therefore, patents and publications are merely used as indicators.

Following the logic of patents and publications as proxies for awareness in emerging technologies, we focused on the question *is the emerging technology of nutrigenomics a hot spot?* Statistics of absolute and relative growth in the number of (nutri-)genomics patents and publications were extracted from databases based on the classifications discussed below. The data were then analysed per country to study whether there are any differences that can influence or are influenced by country-specific circumstances or policy strategies. The comparison of countries based on growth rates or absolute volumes of R&D output does not unpack country-specific and technology-specific differences in the inclination of companies to produce R&D output because they are not compared to each other's specialisation. To include these country-specific and technology-specific differences, the revealed technological advantage (RTA) indicator is used (Patel and Pavitt 1987; Hightower and Soete 1995; Vertova 2001; Cantwell and Santangelo 2002; Mahmood and Singh 2003). The RTA is an index that shows the extent to which a country I is specialised in a technology or sector J. The RTA is calculated by the national share of patenting (P) in that particular sector divided by the national share of patenting in all sectors. A value above unity means a relative specialisation of a country in that technological area, while a value below 1 reflects a relative under-specialisation.

$$RTA_{IJ} = \left( \frac{P_{IJ}}{\sum_{J} P_{IJ}} \right) \Bigg/ \left( \frac{\sum_{I} P_{IJ}}{\sum_{IJ} P_{IJ}} \right)$$

A standardised or normalised version of this formula is the NRTA=(RTA–1)/(RTA+1), which keeps the values between -1 and 1. In the next paragraph we focus in detail on the method used for the patent analyses and the results (§3.5.2). In §3.5.3 we take a closer look at the methods and results of the publication analyses.

### 3.5.2 Patent analysis and results

The major challenge regarding statistical analysis of patent data lies in the proper definition of fields in order to retrieve statistically representative samples (Hinze and Schmoch 2004). When defining technology fields, roughly three different strategies can be deployed:

1. Classification based on the International Patent Classification (IPC) classes;
2. Classification based on keywords;
3. A combination of these two strategies.

The IPC is an internationally agreed, highly hierarchical structure of sections, classes, subclasses, groups, and subgroups into which patents are subdivided. One of the disadvantages of using IPC classes is its inertia: new emerging technologies, such as nutrigenomics, are difficult to file under one specific class, because the class structure is only revised every seven years[23].

Still, the IPC classes served as a starting point for determining the nutrigenomics field. Even though a specific nutrigenomics classification has not been introduced, a proper and often-applied search strategy is to define fields by the cross-section of two different pools of IPC classes (Hinze and Schmoch 2004). For example, the nutrigenomics field combines nutrition with genomics. This cross-section is shown in Figure 14. For the selection of IPC classes an iterative process was used: i) drawing upon experience of previous patent research in the field of biotechnology (OECD 2004; Reiss, Hinze et al. 2004); ii) scanning the International Patent Classifications books; and iii) interviewing experts to discuss keywords that are used in the genomics context and subsequently checking in the Espacenet database whether all relevant IPC classes were included and whether those included were relevant. An overview of the IPC classes used is shown in Annex I.



The patent search was conducted in the Questel database that incorporates patents from both the European Patent Office (EPAT; so-called EP applications) and the World Patents Index (WPI/L; so-called WO applications). For the co-patent analysis patents were retrieved from the Espace Access. The process from patent application to granted patent can take years. Using patent applications has the advantage that the newest entries are taken into account, which is of special interest when studying emerging technologies. In the end, some of these patent applications might not be granted. However, since we are not interested in specific de facto granted patents but in relative differences between technologies this does not present a problem. The search is limited to the European countries, the United States, and Japan within the time span of 1990 to 2002. Since the patent analyses were performed as part of an international research

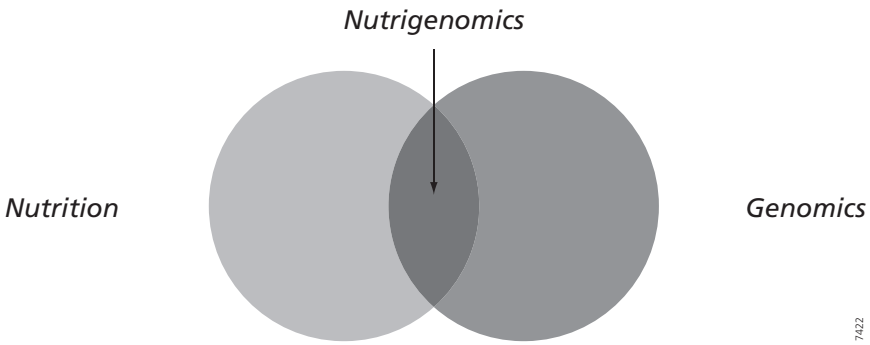


**Figure 14** Cross-section of genomics and nutrition yielding the constructed field nutrigenomics (NGx)

23 Identification based on the more dynamic European Classification System (ECLA) or the even more dynamic In Computer Only (ICO) classification was dismissed due to the low level of coverage in available databases.

project in spring 2005, the database is only up-to-date until 2002, because there is a time lack between patent application and incorporation into the database. Relevant patent documents were collected based on primary and secondary IPC classification.

The search resulted in four different overviews: 1) the amount of genomics and nutrigenomics patents over time as compared to the overall trend of all patents; 2) percentage of nutrigenomics co-publications; 3) revealed technological advantage indicators for nutrigenomics for different countries; and 4) subfields *within* nutrition that prove to be nutrigenomics hot spots. For the latter exercise, nutrigenomics was divided into subfields. Nutrition IPC classes were grouped into coherent subjects (also see Table 15 in Annex I): dairy products (indicated by IPC codes A01J, A23C), fats (A23D), plant products (A01G, A01H), coffee and tea products (A23F)[24].

To obtain an overview of the developments in genomics, the numbers of all patents, genomics patents, and nutrigenomics patents per year were plotted as index figures in Figure 15 below. The figure shows an upward trend, which signifies nutrigenomics innovations as a field that is steadily gaining momentum. There is a clear dip after 1999, which might be explained as follows: After the completion of the Human Genome Project a genomics-related patent 'hype' occurred. After this first rush a decrease occurred, which might be related to the fact that there is discussion about the possibility to patent genes. In this line of events the dip might indicate the beginning of a so-called double boom phase: a renewal of attention when the hype was over (Schmoch 2007).

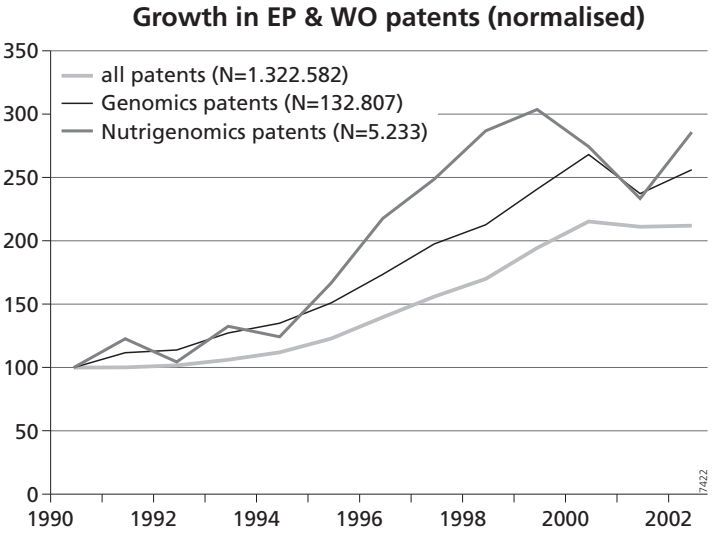


**Figure 15** Trend of applications of EP and WO patents in genomics and nutrigenomics between 1990 and 2002.

24 The subfield 'other' is a collection of the nutrition IPC classes that remained after coherent subfields were constructed. The subfield 'other' does not reflect a clear subfield and is therefore not depicted in the figures.

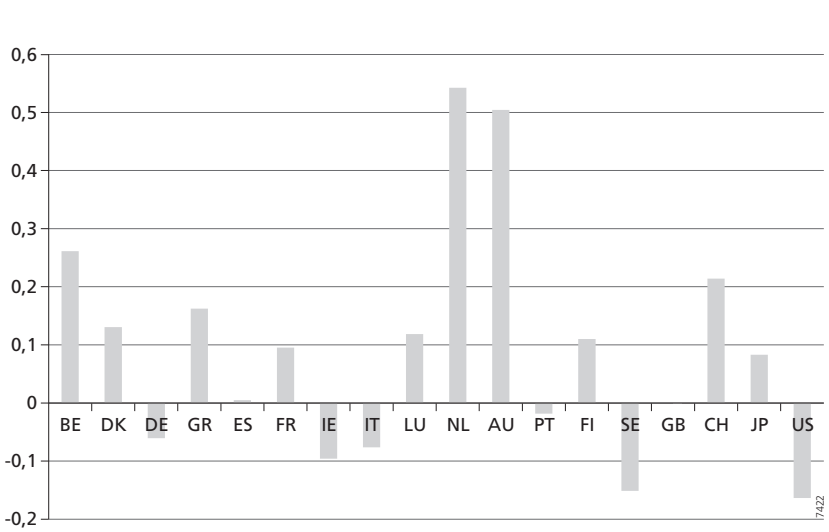


**Figure 16** The NRTA of nutrigenomics EP and WO patents compared to genomics EP and WO patents (period 1990-2002).

An analysis of nutrigenomics patents from 1977-2002 in Espace Access of the top-100 applicants revealed that the 32% of the patents were co-patents of two or more stakeholders, which indicates the collaboration between stakeholders in nutrigenomics.

Based on the nutrigenomics (EP and WO) patents and the total amount of genomics patents for each individual country, the NRTA was calculated, which represents the relative importance of nutrigenomics patents compared to all genomics patents for each country. Figure 16 shows that nutrigenomics is relatively important in the Netherlands and Austria.

Figure 17 illustrates the results for the subfields within nutrigenomics, derived from the division based on different related IPC food classes. Expressed in patent applications, 'fats' show a significant increase in interest.

### 3.5.3 Publication analysis and results

While using patents as an innovation indicator, publications are used as an indicator for scientific interest and activity. Both a publication database and a conference paper abstract database were consulted: Science Citation Index (via ISI Web of Science) and PubMed. All publications were abstracted from these databases in October 2005. In general, both databases were suitable for the analysis of medical related topics as the SCI covers a large number of journals from the field of medical research.

The search strategy focused mainly on using keywords because there was no analogy of IPC classes in the two publication databases. The importance of the nutrigenomics fields was investigated by determining the relative growth of

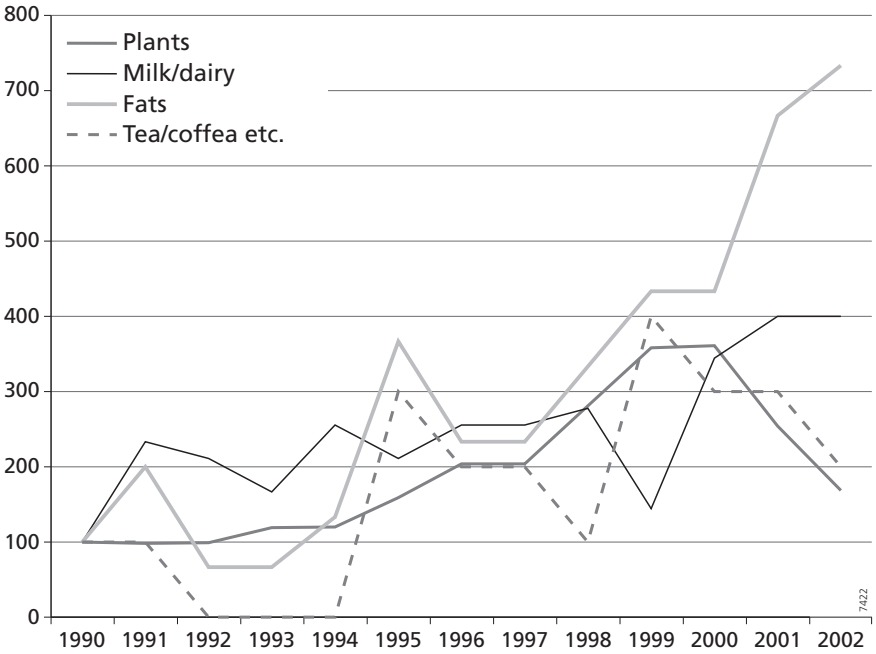


**Figure 17** Interesting subfields in nutrigenomics EP & WO patents based on patent analysis period 1990-2002. Dairy products (indicated by IPC codes A01J, A23C), fats (A23D), plant products (A01G, A01H), coffee and tea products (A23F).

publications in this area. The first strategy to construct a pool of nutrigenomics publications was by using 'nutrigenomics' terms as search words (i.e. 'nutrigenomic(s)', 'nutrigenetic(s)'). The advantage being that the included data had a high probability of really belonging to that field. The second strategy was using a group of keywords that together described the nutrigenomics field. These keywords were collected by scanning relevant literature and reviewing them by interviewed experts in the field. The strategies and keywords are summarised in Annex I, which also contains the resultant numbers of publications. Moreover, an attempt was made to combine the results of the two strategies.

With regard to the validity of the search results, it was important to determine whether the publications that were found belonged to the emerging technology of nutrigenomics. It was assumed that the publications obtained by the 'keyword' search strategy (i.e. 'nutrigenomic(s)', 'nutrigenetic(s)') comprise no false positives, i.e. had a recall of 100%. On the other hand, the chance of publications being 'missed' or not included while they should have been, was expected to be high. In other words, the level of precision was rather low. In fact, articles about nutrigenomics do not necessarily have to feature the nutrigenomics keywords in their titles or abstracts; sometimes the nutrigenomics keywords are only mentioned in the main text. For the combined strategy, the amount of false positives was estimated by taking a sample. The titles, keywords, and abstracts of these publications were scrutinised. For nutrigenomics the recall was 33% (with $p = 0.1$). The resulting recall percentage was not impressive and might easily have led to wrong conclusions. Therefore, we chose

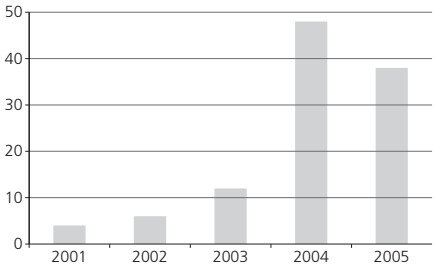


**Figure 18** Number of nutrigenomics articles over the period 2000-2005(N=108)

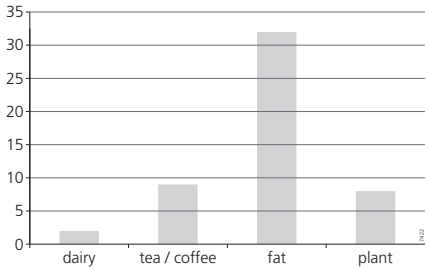


**Figure 19** Number of nutrigenomics articles on dairy, tea/coffee, fat and plants over the period 2002-2005 (N=51)

to work with the results from the first strategy, a search population with a high recall. We also crossed the set of resulting publications with keywords based on expert interviews in order to obtain nutrition-specific subfields. This gave us insights into hot spots within nutrigenomics.

The first nutrigenomics articles were written in 2001[25]. Since then a clear exponential growth can be seen until 2004 (Figure 18). The 'drop' after 2004 is due to the fact that the publication analyses were performed as part of a research in spring 2005 and therefore only the publications in the first quarter of 2005 were taken into account. 66% of the nutrigenomics articles were co-publications.

Also, for the publication data an analysis was performed that shows the attention of publications per subfield of nutrigenomics (Figure 19). These resulted in top rankings for fats and coffee/tea products within nutrigenomics.

### 3.5.4 Summary of the scientometric findings

We observed a general upward trend in scientific articles and patent applications for nutrigenomics, which shows a growing interest in nutrigenomics. There is a good start for patent applications in absolute numbers and we see a significant positive growth compared to all patents. Expressed in patents and publications, nutrigenomics is lighting up as a hot spot, which can be concluded from Figure 15.

Comparison of genomics patents using the NRTA indicator shows that nutrigenomics is especially strong in the Netherlands and Austria. For the Netherlands the findings are hardly surprising since the food and agro-businesses have historically been major drivers of the Dutch economy (Ministerie van Economische Zaken 2004).

The most important subfields within nutrigenomics are summarised in Table 3 for both publications and patents searches. When the results of the patent and publication searches are compared it appears that one subfield is a hot spot both in the patent and in the publication ranking. This is the case for fat products.

25 This supports the statement by Ghosh that nutrigenomics appears to be a 21st century term (Ghosh, Skinner et al. 2007) (see §3.2). NB: The nutrigenomics patent search was based on cross sections of nutrition and genomics, which yielded nutrigenomics patents before 2001 (see Figure 14).

**Table 3** Most important nutrigenomics subfields based on (relative growth of) patents and (absolute number of) publications.

| | Nutrigenomics patents | Nutrigenomics publications |
|---|---|---|
| 1 | Fats | Fats |
| 2 | Dairy products | Tea and coffee products |
| 3 | Tea and coffee products | Plant products |
| 4 | Plant products | Dairy products |

Of the patents and publications, 32% and 66% were respectively co-patents and co-publications, which indicates collaboration and interactive learning regarding nutrigenomics between stakeholder.

## 3.6 Conclusion

Nutrigenomics is the newest research phase in nutrition research that became possible through the Human Genome Project. Several synonyms and definitions are used for nutrigenomics. For our research we use the term *nutrigenomics* for all research into the relationship between genomes, nutrition and disease (risk) and the future applications that might result from that research. For the time being there are no nutrigenomics applications commercially available, but there are high expectations surrounding nutrigenomics in terms of personalised nutrition and disease prevention and treatment. The expected applications are i) functional foods, ii) nutrigenomics research as a process innovation for the substantiation of hard claims on functional foods, and iii) nutrigenomics tests that can be used for life style advice. In order to arrive at these applications, complementary knowledge on genomics, nutrition and disease, and the expertise on related research techniques have to be combined in order to learn and innovate. Based on this, mutually dependent stakeholders formed nutrigenomics consortia in which they interact and learn from each other. Since we are interested in interactive learning in emerging technologies we will focus on these nutrigenomics consortia (see §4.5).

Through the scientometric analyses we observed an increase in both publications and patents in the emerging field of nutrigenomics. The analysis showed that nutrigenomics is a hot spot which draws attention of science and industry. The presence of co-publications and co-patents indicates collaboration and interactive learning within the emerging technology of nutrigenomics. Therefore, the attention devoted to the emerging technology of nutrigenomics by science and industry and the presence of interactive learning, makes the emerging technology of nutrigenomics interesting setting to explore interactive learning.

# 4 Research design

In order to gain insight into interactive learning in emerging technologies we formulated the following leading research question:

*How can interactive learning in emerging technologies be conceptualised, and how can this conceptualisation provide insights into interactive learning between heterogeneous stakeholders in nutrigenomics?*

In order to answer this research question we have arranged the research and this book in two parts: development of the FILET is explained in Part I and exploration of the FILET in Part II. First we give a synopsis of the methods used in Part I and an outline of the 'intermezzo' where we elaborated on the emerging technology of nutrigenomics (§4.1). The remainder of this chapter presents the methods used in Part II. We present the case study methodology and argue why this is the appropriate research method for the purpose of the empirical part of our research (§4.2). We then present a list of candidate cases (§4.3), formulate the selection criteria (§4.4), and select cases on the basis of the list and the selection criteria (§4.5). In (§4.6) we present an analytical framework and will operationalise this framework (§4.7). This framework is used in the analysis of the case studies in the empirical chapters. The data gathering is presented in §4.8. In §4.9 some concluding remarks will be presented.



## 4.1 Methodological synopsis of previous chapters

In Chapter 2 we constructed the Framework for Interactive Learning in Emerging Technologies (FILET). This chapter was based on a literature review covering three bodies of knowledge: literature on innovation, interactive learning and proximity respectively. Journals addressing these bodies of knowledge include Research Policy, Technological Forecasting and Social Change, International Journal of Innovation Management, Regional Studies, Journal of Economic Geography and the International Journal of Foresight and Innovation Policy. In Chapter 3 we discussed the emerging technology of nutrigenomics and argued why this subfield is a good candidate for research in interactive learning in emerging technologies. This chapter was based on explorative interviews with nutrigenomics experts and stakeholders (see Annex II), a literature review, and a scientometric analysis. This provided useful insights into nutrigenomics developments. Furthermore, information was gathered through a review of nutrigenomics-related scientific articles in e.g. the Scopus[26] database. Journals covering nutrigenomics articles include Current Opinion in Biotechnology, Proceedings of the Nutrition Society, European Journal of Clinical Nutrition, Diabetes Care, Nutrition, Trends in Food Science & Technology.

26 www.scopus.com

Additionally we performed a scientometric analyses. This research method was explained at length in §3.5. The scientometric analysis helped us to obtain insight into nutrigenomics patenting and publications over time and to assess the attention devoted by science and industry to nutrigenomics. Nutrigenomics showed to be a hot spot in which research is undertaken in collaboration between stakeholders, as indicated by the presence of co-publications and co-patents. This makes the emerging technology of nutrigenomics an interesting field to study interactive learning.

## 4.2 Case study methodology

Interactive learning in emerging technologies is a phenomenon that occurs in real life. The phenomenon is socially embedded and it is not possible to take it out of this context (as one would do in a lab experiment in a controlled environment). In these real-life phenomena the boundaries between the phenomenon and the surrounding social context might not be clearly evident, and alternative and/or additional mechanisms might also be of importance. Case studies emphasise the rich real life of phenomena and their surrounding context. Yin (2003, p13) defines a case study as *"an empirical inquiry that investigates a contemporary phenomenon within its real-life context, especially when the boundaries between phenomenon and context are not clearly evident."* Not only are case studies the preferred research method for the study of real-life phenomena, case studies are also of importance when building a theoretical framework since "*a theory-building approach that is deeply embedded in rich empirical data, building theory from cases is likely to produce theory that is accurate [and] interesting*" (Eisenhardt and Graebner 2007). Given the absence of clear boundaries between interactive learning and its social context, the impossibility to study this real life phenomenon in a controlled environment and the possibilities the case study approach offers in theory building, the case study becomes the preferred research method for the exploration of interactive learning in emerging technologies.

Regarding case studies we can differentiate between single and multiple case studies. A single case study can give profound insight into a phenomenon in real life, but *"the theory is better grounded, more accurate, and more generalisable (all else being equal) when it is based on multiple case experiments"* (Eisenhardt and Graebner 2007). The advantage of multiple cases is that findings of the first case can be observed in a different setting and compared and complemented with findings resulting from the other case studies. Therefore, multiple cases are important and insight provoking, not leading to immediate rejection but adaptations of the theory. A theory's *"value is to cut through idiosyncrasies and unearth similarities across cases"* (Siggelkow 2007). As such, multiple case studies result in a more superior – i.e. parsimonious and thus more robust and general – theory (Eisenhardt and Graebner 2007). The appropriate cases are selected in §4.5 from a list of candidate cases (§4.3) with the help of selection criteria (§4.4).

Anticipating the following sections we present a graphical presentation of the case study method in Figure 20.

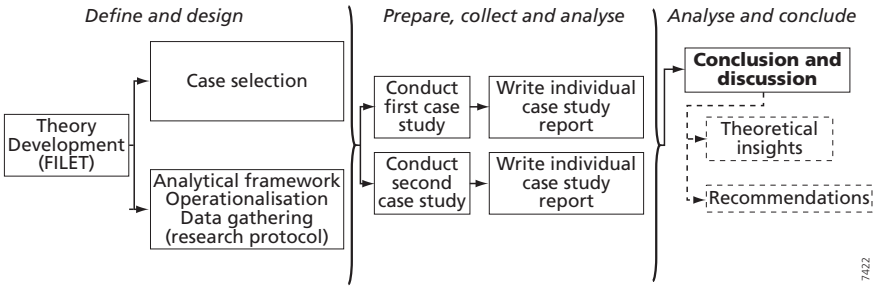


**Figure 20** Graphical overview of the case study method (adapted from COSMOS Corporation as reported in (Yin 2003))

## 4.3 Candidate cases

We are interested in interactive learning in emerging technologies and consequently must focus on 1) an emerging technology and 2) the locus of interactive learning within this emerging technology (i.e. the unit of analysis).

First, a technology is an emerging technology when it complies with three criteria: i) the absence of a common definition or a dominant design and (hardly) any commercially available applications (Utterback 1994), ii) uncertainties and open ends about future applications and related expectations (Nelson and Winter 1977), and iii) a visible increase of linkages between stakeholders in the form of networks (Van Merkerk and Van Lente 2005). In Chapter 3 we saw that nutrigenomics meets these three criteria: there is discussion on the definition of nutrigenomics (§3.2), there are no applications available but there are expectations in terms of future applications (§3.3), and we observed the formation of networks of nutrigenomics stakeholders (§3.4). Also these stakeholders themselves perceived nutrigenomics as an emerging technology (Fogg-Johnson and Kaput 2003; Mutch, Wahli et al. 2005; Kaput, Perlina et al. 2007). Additionally the scientometrics analyses (§3.5) showed that nutrigenomics is a hot spot. Since nutrigenomics is an emerging technology and a hot spot, it is a suitable field for the study of interactive learning in emerging technologies.

Second, we have to find the locus of interactive learning in an emerging technology. As we stated above, interactive learning is a real-life phenomenon and the boundaries between the phenomenon itself and the surrounding social context might not be clearly evident. For the focus of our research we must first set the boundaries for our unit of analyses. According to Tödtling, Lehner et al. (2008), when studying the processes of interactive learning, a distinction can be made between formal (e.g. affirmed in a contract) and informal relations between the stakeholders (Table 4). Informal collaborations are very difficult (if not impossible) to identify because they are often not visible to the outside world. Formal networks often actively present themselves for example through websites. Therefore, the unit of analyses is the interactive learning process within formal networks of stakeholders.

High expectations about the scientific developments in nutrigenomics have stimulated the formation of various consortia of stakeholders (Kaput, Ordovas et al. 2005). Table

**Table 4** Settings and knowledge interactions in the innovation process as distinguished by Tödtling, Lehner et al. (2008)(bold by RV)

| Setting | Knowledge interaction | |
|---|---|---|
| | **Static exchange of ready pieces of knowledge** | **Interactive learning** |
| Formal | Market relations | Cooperation/***formal networks (i.e. nutrigenomics consortia***) |
| Informal | Knowledge externalities and spill-overs | Milieu/informal networks |

5 presents an overview of the eight known nutrigenomics consortia worldwide. The list is based on Afman and Müller (2006), an expert interview (interview 2006-05-10) and snowballing: during the explorative interviews and case studies, interviewees were asked whether they knew any other nutrigenomics consortia. This list functions as a comprehensive list of possible case studies from which suitable cases can be selected. Before doing so, we formulate selection criteria.

## 4.4 Case study selection criteria

The purpose of the empirical research is to explore the Framework for Interactive Learning in Emerging Technologies (Chapter 2). Therefore, cases are not selected randomly but because *"they are particularly suitable for illuminating and extending relationships and logic among constructs"* (Eisenhardt and Graebner 2007). This is called *theoretical sampling*. Cases are chosen because they generate theoretical insights into interactive learning in emerging technologies taking the developed FILET as a starting point. From the list of nutrigenomics consortia we have to select cases that are suitable for our study. Therefore, we formulate the following selection criteria:

1. As explained in the foregoing, a multiple case study approach is chosen for *"replication, extension of theory, contrary replication, and elimination of alternative explanations"* (Eisenhardt and Graebner 2007)[27]. For the initial exploration of the FILET we focus on replication and therefore we are interested in similar cases. Here, similarity is a relative notion that is determined by the comparison of the properties of the consortia.
2. An indication of interactive learning outcome (i.e. interactive scientific knowledge and the realisation of the shared vision), which is an indication that interactive learning occurred. Therefore, we make a quick scan of (co-)patents en (co-) publications and the shared vision[28] as stated in e.g. annual reports and consortia websites.
3. The core business of the consortium must be within the emerging technology of nutrigenomics.
4. The availability of empirical data and the possibility to collect that data for the analyses through e.g. interviews, websites, publications and websites.

27 Here, in their work, Eisenhardt and Graebner refer to (Yin 1994).

28 The co-construction and realisation of the shared vision can only be through the unravelling of the interactive learning process during the actual case study.

**Table 5** Formal networks in nutrigenomics: consortia. Based on Afman and Müller (2006), complemented by RV

| Consortium | Country | Focus | Website |
|---|---|---|---|
| Nutrigenomics Consortium | The Netherlands | Metabolic syndrome Early biomarkers | www.nutrigenomics.nl/ngc/ |
| NCMHD Center of Excellence for Nutritional Genomics | USA | Personalized diet Diet-gene interactions | nutrigenomics.ucdavis.edu |
| Network of Excellence in Nutrigenomics (NUGO) | Europe (EC) | Establishment of a European Nutrigenomics Research Network (research, training, standardisation) | www.nugo.org |
| Centre of Excellence in Nutrigenomics | New Zealand | Crohn's disease New food bioactives | www.nutrigenomics.org.nz |
| Functional Food Genomics | Japan | Biomarkers and bioactive food ingredients | n/a |
| Nutrigenomics Network – Competence Network Metabolic Syndrome | Germany | Complex diseases Gene-diet interactions | www.nutrigenomik.de |
| Danish Platform in Nutrigenomics | Denmark | identify and support Danish positions of strength in the field of nutrigenomics | www.lmccongress.dk/index.php?id=492 |
| DSM, European Genetic Alliances' Network (EGAN) and the International Genetic Alliance (IGA) | The Netherlands | collective activities to increase the level of awareness and knowledge of patients, patient organisations and the general public and collaborate in projects | n/a |

## 4.5 Case selection

In this section we apply the four selection criteria (§4.4) to the list of candidate cases of formal nutrigenomics consortia (Table 5).

***Selection criterion 1 – similarity***

The Danish Platform in Nutrigenomics turned out to be unsuitable because it was a one-man initiative and therefore could not qualify as a consortium (interview 2007-08-15). NUGO is a EU-funded Centre of Excellence, and therefore not a typical consortium. This would make NUGO an a-typical case and therefore was not selected as a case study.

***Selection criterion 2 – interactive learning outcome***

The DSM/EGAN/IGA consortium was excluded because explorative interviews (interviews 2007-02-23 and 2007-05-30) for this candidate case showed that there had been no interactive learning outcome (as yet).

***Selection criterion 3 – nutrigenomics as core business***

The Japanese consortium was not selected as it turned out to be very difficult to find information about this consortium due to the absence of a website. Therefore it could not be assessed whether the Japanese consortium focuses on nutrigenomics or functional foods.

***Selection criterion 4 – availability and accessibility of empirical data***

This leaves us with the USA, New-Zealand and the European consortia. From a data collection and accessibility perspective the European countries are more easily accessible and, therefore, we focus on the Netherlands, and Germany.

The Dutch Nutrigenomics Consortium (DNC) and the German Competence network Metabolic Syndrome (CMS) both qualify as suitable cases because they fulfil the selection criteria (Table 6):

1. The cases are similar in the sense that they are both consortia of heterogeneous stakeholders with complementary backgrounds in nutrigenomics-related knowledge fields;
2. The DNC and CMS generated interactive learning outcome;
3. Their actual focus is on nutrigenomics;
4. Due to their location in the Netherlands and Germany, these consortia are very convenient cases for the collection of empirical data.

**Table 6** Overview of focus and outcome of selected cases[a]

| Consortium | Stakeholders | Outcome | Focus |
|---|---|---|---|
| DNC | WCFS – nutrition<br>CMSB – genetics | • 16 scientific articles<br>• *"The Nutrigenomics Consortium aims to increase our understanding of the events unfolding during metabolic stress, with the ultimate objective to discover and validate molecular biomarkers for the early detection of metabolic stress and to identify and develop novel food components for dietary management and prevention of metabolic stress"*(www.genomics.nl 2008). | Metabolic Stress |
| CMS | Charité-Universitätsmedizin Berlin – hypertension<br>Dife – mouse studies<br>Max-Planck Institute – SNPs analysis methods | • 28 scientific articles<br>• *"Identifying functionally relevant candidate gen-polymorphisms for high blood pressure and determination of individual genetic risk profiles as a basis for innovative nutri- and pharmacogenomics therapy in high blood pressure patients."*(Netzwerk Nutrigenomforschung Berlin/ Brandenbrug) | Hypertension as part of the Metabolic Syndrome[b] |

a. An extensive overview of the focus and outcome of the consortia is presented in the case study chapters.
b. As we showed in Chapter 3 the Metabolic Syndrome/Metabolic Stress and nutrigenomics are affiliated with each other. Therefore, the research within the cases can be typified as nutrigenomics research.

## 4.6 Analytical framework

For the case studies we use an analytical framework that also functions as a blueprint for the structure of the case study chapters. The analysis consists of three steps. First the interactive learning outcome is identified (both the interactive scientific knowledge outcome and realisation of the shared vision). The second step focuses on the influence of the interactive learning process on the learning outcome. In the third and final step the influence of the conditions for interactive learning on the interactive learning process are put central (Figure 21).

In the analytical framework the sub-questions[29] act as the starting point for the case studies. Through these research questions a link is established between the empirical data and the theoretical concepts in the FILET (Table 7). Before the sub-questions are addressed each case study starts with an introduction of the consortium in order to obtain an understanding of the context from which the consortium originated and the context in which the consortium operated. Conclusions are drawn and discussed in the last section of the case studies.[30]

## 4.7 Operationalisation

In this section we operationalise the theoretical concepts of the FILET. The operationalisation itself builds a bridge between the theoretical concepts on the one hand, and the observations, experiences and language used by the stakeholders in the case studies on the other. The operationalisation attempts to correspond as closely as possible with the theoretical concepts in terms of empirical variables (i.e. construct validity (Yin 2003, p.35)). Therefore, we incorporate frequently used variables in interactive learning and proximity literature. We operationalise all concepts for each FILET building block (i.e. outcome, process and conditions). For the codified outcome, well-known variables such as publications and patents are used. We are also interested in the tacit outcome, and for this dimension it is more difficult to find clearly defined empirical variables. To cope with this problem in § 4.7 multiple empirical variables are used for operationalisation of the same theoretical concept. This allows for data triangulation, which increases the construct validity (Yin 2003, p.99). The

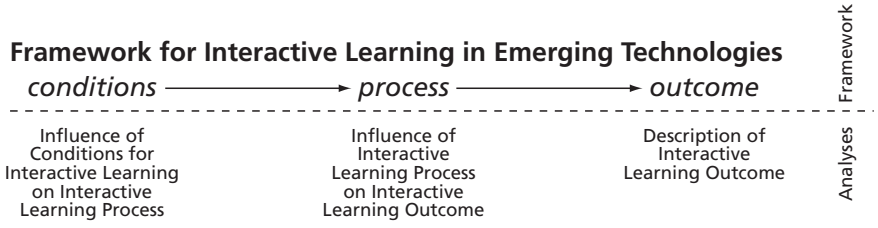


**Figure 21** The three building blocks of the FILET

29 I.e. sub-questions 6, 7 and 8 that we formulated in Chapter 1.

30 Theoretical conclusions regarding the FILET are drawn in the Chapter 7.

**Table 7** Analytical framework of the case studies

| | |
|---|---|
| | **Introduction** |
| | • How did the consortium come into existence?<br>• What is the context in which the consortium existed?<br>• How is the consortium related to other nutrigenomics activities (within the country under study)? |
| | **The interactive learning outcome of the consortium** |
| *6. What was the interactive learning outcome of the consortium?* | • Did the consortium provide an interactive scientific knowledge outcome? – This question is asked in order to make a distinction between the reported scientific outcome of the consortium (e.g. publications and patents) and the part of this outcome that was actually influenced by the interactive learning process.<br>• Is there a shared vision?<br>  • What was the dominant problem definition?<br>  • What was the goal?<br>  • What were the objectives?<br>  • What was the approach?<br>• Where and how is this shared vision propagated?<br>• What are the stakeholders' (i.e. interviewees) opinions about the shared vision?<br>• To what extent was the shared vision *realised* at the end of the consortium? |
| | **The interactive learning processes and how it influenced the interactive learning outcome** |
| *7. How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process??* | • Who was the prime mover and how did he/she influence the co-construction and realisation of the shared vision and the interactive scientific knowledge outcome?<br>• How did the network formation take place and how did it influence the co-construction and realisation of the shared vision and interactive scientific knowledge outcome?<br>• Was there an intermediary and how did he/she influence the co-construction and realisation of the shared vision and the interactive scientific knowledge outcome?<br>• Which knowledge flows were perceptible in the consortium and how did they influence the co-construction and realisation of the shared vision and the interactive scientific outcome? |
| | **The conditions for interactive learning and their influence on the interactive learning process** |
| *8. How were the elements of the interactive learning process influenced by the conditions for interactive learning?* | • How was geographical proximity influencing the elements of the interactive learning process (i.e. prime mover, network formation, intermediary, and knowledge flows)?<br>• How was cognitive proximity influencing the elements of the interactive learning process?<br>• How was regulatory proximity influencing the elements of the interactive learning process?<br>• How was cultural proximity influencing the elements of the interactive learning process?<br>• How was social proximity influencing the elements of the interactive learning process?<br>• How was organisational proximity influencing the elements of the interactive learning process? |
| | **Conclusion and discussion** |
| | • Conclusion and discussion |

operationalisation is summarised in Table 8 at the end of this section. The variables are printed in italics in the main text.

### 4.7.1 Interactive learning outcome

The interactive learning outcome consists of the *interactive scientific knowledge outcome* and the *realisation of the shared vision.*

#### *Interactive scientific knowledge outcome*

The scientific knowledge outcome can be subdivided in a codified and a tacit outcome. When looking at the interactive learning outcome, only those scientific knowledge outcomes are taken into account that resulted from interactive learning. In their research on collaboration between French academic organisations and firms (Goddard and Isabelle 2006) showed that the most frequent outcome of these collaborations are *(co-)publications*. Hereby, co-authorship of articles refers to collaboration and interaction. The same argument holds for *co-patents*. However, only identifying co-publications and co-patents as the interactive scientific knowledge outcome would be too limited. In practice, not all interactive learning between stakeholders has led to co-publications and co-patents. Not all inter-organisational collaborations automatically result in co-publications because the *"way of rewarding collaborative contributions may vary"* (Laudel 2001). When looking at patents, for administrative reasons one stakeholder might apply for a patent and other stakeholders are often given a licence because the patent would not have been possible without the interactive learning between the stakeholders. Thus, only looking for co-publications and co-patents would not give a complete view of the interactive learning outcome resulting from the stakeholders' collaboration. Therefore, in order to obtain a better insight into the interactive scientific knowledge outcome, the interviewees are asked more in-depth questions about the scientific knowledge outcome, especially the extent to which the outcome was the result of interactive learning. This also allowed us to gain insight into the tacit scientific knowledge outcome that did not result in a co-patent or co-publication, but would not have existed without interactive learning.

With regard to consortia it is sometimes difficult to assess which articles and patents are an outcome of the consortium under study. Consortia often have a complex structure comprising different stakeholders, each with their own complex internal structure (e.g. departments, research groups etc.), with numerous research projects and contacts with other actors outside the consortium. Consortia often publish annual reports and evaluation reports and also mention their achievements (e.g. patents and publications) on their websites. We will use these sources in order to obtain the most complete possible overview of the (codified) outcome of the consortia.

Cooperation in consortia can also result in agreements on s*tandardisation* regarding how to perform experiments. Standardisation is a codification process that makes knowledge exchange easier and can be regarded as an interactive learning outcome. Also *applications* (e.g. new functional foods or dietary services) can be the result of the interactive learning process between stakeholders.

Some knowledge cannot or has not yet been codified due to the latency time between discovery and codification in a publication or patent. Tacit knowledge is very important, especially in emerging technologies in which not all knowledge has been

codified, and in which complex knowledge often needs tacit explanation (Johnson, Lorenz et al. 2002). At the same time, operationalising tacit knowledge is inherently difficult (Collins 1974, p167) because it is knowledge that resides within people. We employ two strategies in order to find out whether the consortium resulted in an increase of tacit knowledge. Tacit knowledge manifests itself as increased *know how* and *experience* of stakeholders, and the stakeholders themselves can assess whether or not they gained new scientific knowledge through the collaboration. Therefore, the first strategy is to ask interviewees explicitly about the increase of know-how and experience that can be seen as a result of the collaboration. This strategy might result in socially desirable answers by (some) interviewees. This bias can be reduced up to a certain degree by the triangulation of multiple interviews (also see §4.8). A second strategy to study an increase in tacit knowledge among the stakeholders is to identify situations in the case studies that indicate the *ability* of stakeholders to *solve a problem* at a later stage of the collaboration; a problem they could not have overcome by themselves before the collaboration. An example in nutrigenomics might be the use of new 'omics' technology[31] by stakeholders that are unfamiliar with this – for them – new technique. At the start of the collaboration stakeholders might have difficulties using a new technique, but they might overcome those difficulties through interactive learning with other stakeholders who were already familiar with the technique.

#### *Realisation of the shared vision*

At the beginning of a collaboration stakeholders co-construct a shared vision. This shared vision entails the *dominant problem definition* (Vergragt 1988), *common goal* (Checkland 1988; Vergragt 1988; Smits 2005), *objectives* (Argyris and Schön 1978, p3) and the *approach* taken to realise them. For example, the problem might be concerned with a nutrition-related genetically predisposed disease and the goal of the consortium might be to find a solution to that problem. The objectives that the consortium set itself contribute to the fulfilment of the goal. Therefore an approach might be arranged in the form of a division of labour/research among the stakeholders (e.g. research strands or work packages). This shared vision is often propagated on consortia websites, reports and handouts (codified). Also, stakeholders can make statements about this shared vision (tacit and codified).

The stakeholders can *realise their shared vision* through the research within the consortium. Through new scientific insight it becomes evident to which extent the stakeholders are able to realise their shared vision. To find out the extent to which the shared vision has been realised by the stakeholders through the interactive learning process, we assess whether the stakeholders carried out the research steps in their approach and whether they achieved their objectives and goal.

### 4.7.2 Interactive learning process

The elements of the interactive learning process are the *prime mover, intermediary, network formation,* and *knowledge flows*.

31 See §**3.2** for an introduction into 'omics' technologies.

***Prime mover***

The prime mover is defined as the *stakeholder taking the initiative* to interact with other stakeholders and bring them together on the same subject (Kerkhof and Wieczorek 2005; Leeuwis, Mierlo et al. 2005; Smits 2005). The prime mover is driven by a sense of urgency and mutual dependency. The sense of urgency is based on the perceived problem the prime mover wishes to address and the perceived potential of the emerging technology. At the same time, a mutual dependency exists between the prime mover and other stakeholders regarding complementary knowledge (e.g. genomics and nutrition) and resources (e.g. research facilities). Driven by this sense of urgency and mutual dependency the prime mover will look for other stakeholders. It might be the case that several actors fulfil the role of prime mover more or less simultaneously. The prime mover is identified, based on the specific role 'played' by a stakeholder during the formation of the consortium, and also on the statements made by interviewees that designate a stakeholder as the prime mover.

***Intermediary***

An intermediary *"connect[s], translate[s] and facilitate[s] flows of knowledge"* (Van Lente, Hekkert et al. 2003). Since the prime mover takes the initiative and 'connects' the stakeholders, we put the emphasis of the intermediary on *translating* knowledge from one stakeholder to another (Geurts 1993). The intermediary is identified on the basis of the specific role 'played' by a stakeholder during the formation of the consortium and within the consortium, and also on the statements made by interviewees that designate a stakeholder as an intermediary.



***Network formation***

Network formation is the process during which a growing number of stakeholders start to interact more frequently to achieve a shared vision. Network formation is characterised by an *increasing number of interacting actors, increasing linkages between these actors and increasing contact moments* (Van Merkerk and Van Lente 2005).

***Knowledge flows***

In Chapter 2 (§2.2) we used a knowledge taxonomy as heuristic tool (Lundvall and Johnson 1994) in order to distinguish different forms of knowledge that are interchanged between stakeholders in networks within emerging technologies in which complementary knowledge is combined. This heuristic tool is also used to follow the *knowledge flows* between the stakeholders in the case studies. *Know-what* refers to facts (e.g. the ingredients in a product), *know-why* refers to knowledge on scientific principles and laws (e.g. heredity principles), *know-how* refers to skills or the ability to do something (e.g. an experiment), and *know-who* refers to who has which (of the aforementioned) knowledge.

### 4.7.3 Conditions

The conditions for interactive learning are *geographical, cognitive, regulatory, cultural, social,* and *organisational proximity*. In the theoretical chapter (Chapter 2) we observed that the proximities could be measured at different levels (i.e. micro, meso or

macro[32]). We are interested in interactive learning between stakeholders in consortia and therefore we are interested in the measurement of proximities at the meso level. In Chapter 2 we showed that we make one exception for regulatory proximity, for which we focus both on the meso and macro level because collaboration in emerging technologies can also be influenced by regulations at the macro level (see §2.4).

***Geographical proximity***

Geographical proximity is the "*spatial or physical distance between economic actors [e.g. stakeholders]"*(Boschma 2005). At the meso level (i.e. the consortium), absolute geographical proximity is related to the *agglomeration* of stakeholders in a geographical unit (i.e. the same region) (Knoben and Oerlemans 2006).

***Cognitive proximity***

Cognitive proximity is the distance in the cognitive base between stakeholders in the network (Boschma and Lambooy 1999): *"people sharing the same knowledge base and expertise may learn from each other"*(Boschma 2005). Stakeholders with a (partly) similar technological focus share a certain knowledge base. Therefore, there is a cognitive proximity that enables them to absorb new knowledge related to their knowledge base and it becomes easier for them to learn from each other. Closely related knowledge bases facilitate the absorptive capacity: i.e. the ability of an organisation to recognize the value of new, external information, to assimilate it, and to apply it to commercial ends. The absorptive capacity is critical to the innovative capabilities of organisations (Cohen and Levinthal 1990).

The general *technological focus* of the stakeholders (e.g. nutrition or genomics or specific diseases) gives a general impression of their (difference in) knowledge base. *Co-citations* and *cross-citations* in scientific articles and patents refer to closely related knowledge bases. The related knowledge base can also be identified based on the *journals* in which the stakeholders publish their articles. It is assumed that if stakeholders publish in a journal, they will also read that journal. Furthermore, it is assumed that stakeholders publishing in the same journal also read each other's work and thus are familiar with each other's knowledge (fields). The technological focus is based on the organisation's core activities as e.g. expressed on stakeholders' websites and annual reports, and the co/cross-citations are derived through a network analysis using UCINET6 (Borgatti, Everett et al. 1999).

***Regulatory proximity***

At the meso level, close regulatory proximity between stakeholders is demonstrated by *mutual agreements* (Boschma 2005) at the network level, dealing with Non Disclosure Agreements (NDA) and Intellectual Property Rights (IPR) between multiple heterogeneous stakeholders.

As we argued in Chapter 2 (§2.4) besides regulatory proximity at the meso level (i.e. within the consortium), also the regulatory proximity at the macro level (i.e. innovation system) influences the consortium. Regulations, for instance laws, at the macro level can (partly) reduce uncertainty that surround emerging technologies. This

32 Individual stakeholders are operating at the micro level and the innovations system constitutes the macro level; consortia are at the meso level.

can stimulate interactive learning in the emerging technology. Furthermore, research in emerging technologies can also be stimulated or triggered by the availability of governmental funding.

***Cultural proximity***

Cultural proximity is the distance/closeness between informal 'rules' of the stakeholders in the network. It refers to sets of routines and established practices (Edquist and Johnson 1997, p46), norms and habits (Boschma 2005) or ways of working (Tracey and Clark 2003). The cultural difference between science stakeholders and industry stakeholders is reflected in their different outcome foci: Whereas companies are focused on commercialisation and patents, universities are mainly focused on publications. As a result, the difference in incentive structure between science stakeholders and industry stakeholders proxies the cultural proximity (Dasgupta and David 1994; Ponds, Oort et al. 2007). Therefore, we use the *organisational type* (industry or science) for the perceived difference or overlap in culture. Different organisational types denote a cultural distance, whereas similar organisational types denote cultural proximity.

***Social proximity***

Malmberg and Maskell (1999) put extra emphasis on trust because tacit knowledge is transmitted more easily when stakeholders trust each other. Trust, therefore, is often regarded as a capability that supports learning and innovation. Trust refers to a relation of reliance between stakeholders. Stakeholders that trust each other are confident that they will act as they agreed (e.g. not 'leaking' knowledge to parties outside the network). Trust can be derived on the basis of earlier relations or a *shared history*: collaboration in the past encourages stakeholders to cooperate again, which denotes the presence of trust. Trust is also indicated by the mutual *open access to research facilities* and *databases* among the stakeholders in a consortium[33].

***Organisational proximity***

Organisational proximity is *"the extent to which relations are shared in an organisational arrangement"* (Boschma 2005). Organisational proximity facilitates the knowledge creation of individual stakeholders and coordination of the knowledge of all stakeholders. Therefore, organisational proximity has an optimum that lies between total autonomy of individual stakeholders (i.e. *flexibility*) and the total control over the stakeholders (i.e. *coordination*). Since the *"organisational arrangement"* in our study is the consortium itself (meso level), we look at the consortium's organisational structure. The *organisational structure* is determined on the basis of the relations between the stakeholders (both in practice as well as written down in mutual agreements).

33 During the first case study (DNC) the shared history among the stakeholders was assessed and interviewees were asked directly whether they trusted one another. During the second case (CMS) the shared history was again assessed. Then interviewees were asked first whether they had access to each other's databases and research facilities and then whether they trusted each other. Consequently, the presence of trust in practice (indicated by free access) and the opinion of the stakeholders regarding the presence of trust could be assessed.

The operationalisation of the concepts of FILET is summarised in Table 8.

**Table 8** Operationalisation FILET

| Concept | Empirical variables |
|---|---|
| **Interactive learning outcome** | |
| Scientific knowledge outcome | *Codified*<br>• (co-)publications<br>• (co-)patents<br>• standardisation<br>• applications<br>*Tacit*<br>• increase in know-how<br>• increase in expertise<br>• problem solving capabilities |
| Realised shared vision | *Codified* (in e.g. mission statements)<br>• dominant problem definition<br>• common goal<br>• objectives<br>• approach<br>*Tacit* expression by stakeholders about (non-codified) shared vision on<br>• dominant problem definition<br>• common goal<br>• objectives<br>• approach |
| **Interactive learning process** | |
| Prime mover | • stakeholder taking initiative<br>• assigned role by interviewees |
| Intermediary | • stakeholder translating knowledge between other stakeholders<br>• assigned role by interviewees |
| Network formation | • increasing interacting actors<br>• increasing linkages<br>• increasing contact moments |
| Knowledge flows | • know-what (e.g. the ingredients in a (future) nutrigenomics product)<br>• know-why (e.g. genetic principles)<br>• know-how (e.g. an experiment)<br>• know-who (e.g. stakeholders 'holding' the knowledge |
| **Conditions for Interactive learning** | |
| Geographical proximity | • agglomeration of stakeholders in region |
| Cognitive proximity | • technological focus<br>• co-citations and cross-citations<br>• journals stakeholders publish in |
| Regulatory proximity | *Macro level*<br>• laws<br>• funding<br>*Meso level*<br>• mutual agreements |
| Cultural proximity | • type of organisation (i.e. industry or science) |
| Social proximity | • shared history<br>• open access to research facilities and databases |
| Organisational proximity | • organisational structure (=>flexibility and coordination) |

## 4.8 Data gathering

From the questions in the analytical framework (§4.6) and the operationalisation of the theoretical concepts (§4.7) we know which data are required in order to answer the analytical questions. For the analyses of the cases, different types of data are gathered from different sources (Yin 2003, p.86): interviews, scientific articles, patents, grey literature and websites. All data are stored in a 'case study database' per case study[34], which allows reliability tests (Yin 2003, p.37).

General information on (the emergence of) consortia, the stakeholders within consortia and policies surrounding these consortia, is derived from the websites of the consortia and stakeholders and complemented with internal documents (i.e. 'grey literature' like mid term and annual reports) and policy documents. Scientific articles and patents are used to assess the outcome of the consortia. Other publications (e.g. website and news articles) reporting about the consortia are used as complementary sources.

The interactive learning process is mainly assessed through interviews with consortia stakeholders. Interviews make it possible to gather rich empirical data (Eisenhardt and Graebner 2007). Interviewing multiple knowledgeable informants is highly accurate – especially when the topic is of recent date – because it is unlikely that informants will *"engage in convergent retrospective sense making"* (Eisenhardt and Graebner 2007). Triangulation of interviews obviates situations in which stakeholders would give a more positive image than what was achieved in reality. The most knowledgeable respondents of all involved stakeholders in the consortia, research managers (see Annex II), were selected on the basis of their participation in projects and overall understanding of the consortium. Semi-structured questionnaires (see Annex III) are used, which address the concepts and relations in the FILET. At the same time, this semi-structured approach leaves room for the interviewees to address other factors (and as such the boundaries between the real-life phenomenon of interactive learning and its surroundings can be observed). The interviews are recorded, transcribed with F4[35], and a summary is sent to the interviewees for authorisation. In F4 the transcription can be linked to the corresponding time in the audio recording of the interview for future reference. After authorisation, interviews can be coded with Nvivo[36], in which statements by interviewees can be labelled in accordance with the operationalisation: e.g. if an interviewee mentions a stakeholder taking the initiative to form a consortium or actually calls this stakeholder a prime mover, this statement is labelled prime mover (for a coding example see Figure 22). This allows for quick identification of relevant statements involving the prime mover, and the aggregation of these statements. The coding is randomly blind checked by a second researcher, and the two coding schemes for an interview are compared in order to identify similarities

34 Per case study all electronic data (e.g. interview recordings, interview transcripts, scientific articles etc.) are stored electronically and additional hard copy only and/or printed materials are filed.

35 www.audiotranskription.de/english/transcription/audiotranscription-with-f4-/audiotranscription-with-f4.html

36 www.qsrinternational.com/

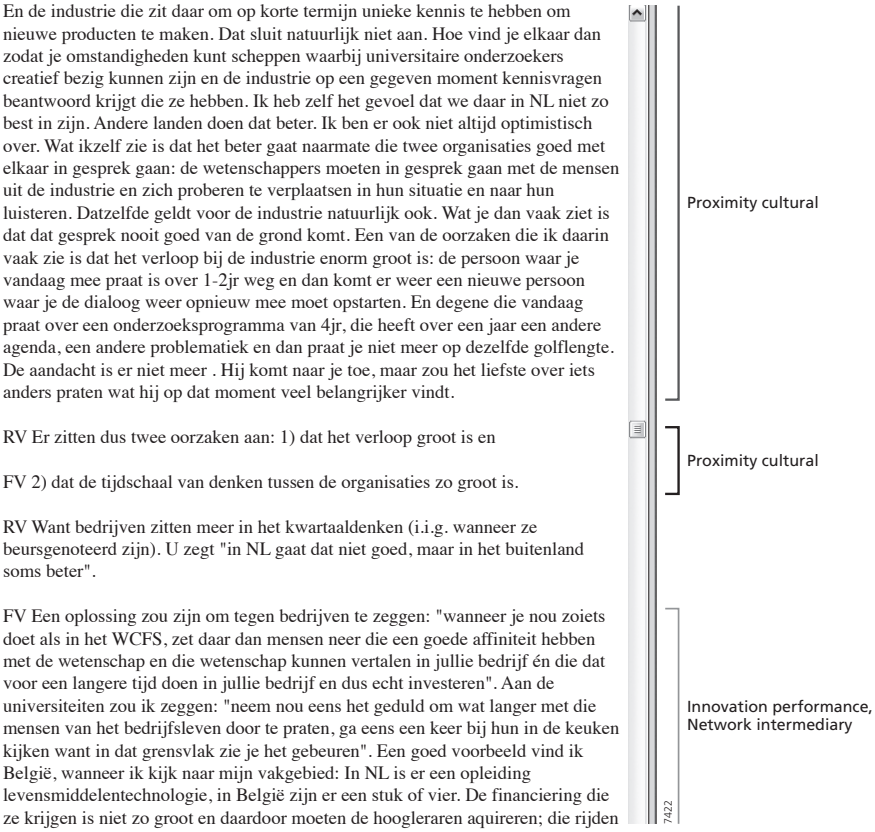


**Figure 22** Coding of DNC interview in Nvivo: transcript (in Dutch) on left side and coding fields on right side. The first paragraph is labelled “cultural proximity”

and differences. This so-called investigator triangulation increases the reliability of the analyses (Yin 2003).

An external expert who is knowledgeable of nutrigenomics and the consortium, but who is not directly involved in the research performed in the consortium that is the subject of the case study, reviews the concept version of the case study that results from the data analyses. The review by the external expert contributes to the construct validity of the research (Yin 2003, p.34).

## 4.9 Conclusion

For the theoretical part of our research we used literature reviews, patent and publication analyses and expert interviews. The goal of our research is the development and exploration of a Framework for Interactive Learning in Emerging Technologies. Based on the fact that interactive learning is a real-life phenomenon with unclear boundaries, the multiple case study method is selected as the most appropriate

research method for the empirical part or our research. Based on the selection criteria applied to a list of candidate cases (Table 5) we selected the DNC and CMS as case studies. For the case studies we use the analytical framework as presented in §4.6. The operationalisation of the theoretical concepts is summarised in Table 8. The analytical framework, operationalisation and data gathering compose a research protocol (Yin 2003, p.67) through which a chain of evidence (Yin 2003, p105) can be traced from raw data through analysis to conclusion and/or back. In the next chapters we present the case studies that were performed with the help of this research protocol.

# 5 Interactive Learning in the Dutch Nutrigenomics Consortium[37]

In this chapter we explore the Framework for Interactive Learning in Emerging Technology (FILET) in the case of the Dutch Nutrigenomics Consortium (DNC). We start with a short introduction of the context in which the DNC originated (§5.1). Hereafter we focus on the three building blocks of the FILET and the relations between the building blocks with the help of three *sub-questions*:

6. *What was the interactive learning outcome of the consortium?*
7. *How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process?*
8. *How were the elements of the interactive learning process influenced by the conditions for interactive learning?*

In §5.2 we describe the interactive learning outcome of the DNC. In §5.3 we turn to the interactive learning process and *how* it influenced the interactive learning outcome. In §5.4 we describe how the interactive learning process was influenced by the conditions for interactive learning. We conclude and discuss the case study findings in §5.5[38].



## 5.1 Origination and context of the DNC

In 2000 the Dutch Government installed the Temporary Advisory Committee Knowledge Infrastructure Genomics[39]. The Committee's task was to advise the Dutch government *"on the necessity and possible scope of investment in the genomics knowledge infrastructure."* In 2001 the Committee concluded that: *"(T)he current level of investment in the Netherlands leaves no room to join (the genomics) development train, so that important social and economic opportunities will be missed. Reinforcement of the genomics knowledge infrastructure is therefore vital, and is certainly in keeping with the Cabinet's ambition to get the Netherlands a pioneering role in the 'Europe of knowledge and innovation'"* (Tijdelijke Adviescommissie Kennisinfrastructuur Genomics 2001).

The Temporary Advisory Committee Knowledge Infrastructure Genomics suggested the establishment of a national coordinating body for the stimulation and build-up of a genomics knowledge infrastructure in the Netherlands. In 2002 the Netherlands

37 A shorter version of this chapter was published in (Moors, Boon et al. 2008)

38 We reflect on the FILET in the final chapter of this book (Chapter 7).

39 In Dutch: Tijdelijke Adviescommissie Kennisinfrastructuur Genomics

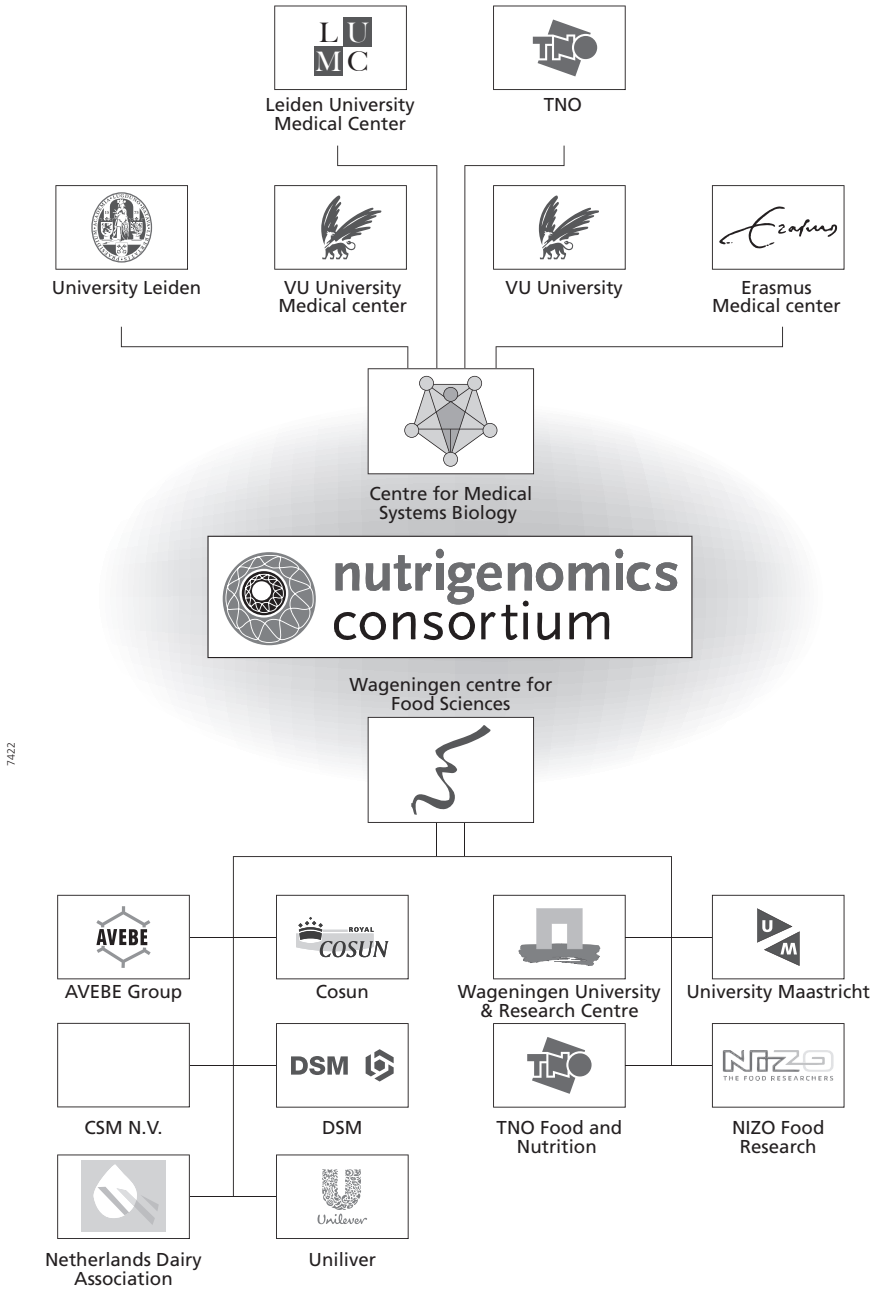


**Figure 23** DNC organogram (Nationaal Regie-Orgaan Genomics 5-8-2007)

Genomics Initiative (NGI)[40] was installed *"to set up a world class (genomics) infrastructure"* (Netherlands Genomics Initiative 2002). The NGI had a total budget of € 311 billion for the period 2002-2008. In this period the NGI funded 11 genomics consortia (Nationaal Regie-Orgaan Genomics 2008). The Temporary Advisory Committee Knowledge Infrastructure Genomics (Tijdelijke Adviescommissie Kennisinfrastructuur Genomics 2001) and the NGI denoted nutrigenomics as a significant area of research, which resulted in the availability of funding for nutrigenomics research. The Dutch Nutrigenomics Consortium (DNC) became one the consortia that was funded.

The Dutch Nutrigenomics Consortium is a consortium of nutrition research organisations and food companies collaborating in the Wageningen Centre for Food Sciences (WCFS), and genetics research organisations collaborating in the Centre for Medical Systems Biology (CMSB). The WCFS and the CMSB started to join forces around 2002 for the purpose of forming a nutrigenomics research collaboration (Figure 23). In 2003 € 11 million was awarded to the Dutch Nutrigenomics Consortium (DNC) by the NGI as match funding. Together with the stakeholders' matching investments within the DNC the total budget for the DNC was € 22 million for the period 2003-2007.

In this section we gave a brief description of the origination and context of the Dutch Nutrigenomics Consortium. For a more elaborate overview of the Dutch genomics infrastructure in general see Propp and Moors (2009). In the following sections we focus on interactive learning within the DNC from 2003 to 2007[41].



## 5.2 Interactive learning outcome of the DNC

In this section we answer the first sub-question as formulated in the analytical framework in §4.6:

6. *What was the interactive learning outcome of the consortium?*

We first describe the interactive scientific knowledge outcome that resulted from the interactive learning process within the DNC in §5.2.1. The realisation of the shared vision covers the shared vision co-constructed by the stakeholders at the start of the DNC in 2003 and the extent to which the stakeholders were able realise the shared vision at the end of the DNC in 2007. This is described in §5.2.2. The findings regarding the interactive learning outcome are summarised in §5.2.3.

### 5.2.1 Interactive scientific knowledge outcome

Interactive scientific knowledge outcome is the scientific knowledge resulting from the interactive learning process that is needed to find answers to specific questions

40 In Dutch: Nationaal Regie-Orgaan Genomics

41 NB: After our case study the NGI entered its second five year period (2008-2012) and the NGI's total budget for this second period increased to approximately € 500 mln. The NGI continued to finance the DNC (www.genomics.nl 12-12-2008).

or – more pragmatic – solutions to problems. Within nutrigenomics this is related to genomics-nutrient interactions and nutrition-related genetically predisposed diseases such as the Metabolic Syndrome. For science-based consortia scientific (co-) publications are the most frequent outcome of these collaborations (Goddard and Isabelle 2006). When an emerging technology becomes more widely applied, (co-) patents and applications also become an outcome of the research activities. Standardisation of how to perform experiments is also a codification process which makes knowledge exchange easier. Besides these codified indicators, an increase in tacit scientific knowledge can also be perceptible in more know-how, expertise and problem solving capabilities.

At the end of the DNC in 2007 an internal document was written that contained an overview of the outcomes of the DNC (Hessing 2007). We use this document as the starting point to describe the interactive scientific knowledge outcome. During its existence (2003-2007) the DNC produced 16 scientific articles (see Annex IV for an overview). Of these 16 articles, six were co-publications. We can distinguish two sorts of co-publications that resulted from the DNC: co-publications of WCFS *and* CMSB stakeholders, and co-publications of either multiple WCFS or multiple CMSB organisations. All co-publications indicate collaboration. Nevertheless, the distinction is made because co-publications between multiple WCFS or CMSB organisations indicate the ability to bridge knowledge gaps within nutrition (WCFS) or genetics (CMSW), and co-publications between the WCFS and CMSB indicate that the 'broader' knowledge gap between nutrition (WCFS) and genetics (CMSB) could be bridged, and that knowledge could be combined (as expressed in the article):

- One publication was a co-publication of the WCFS and CMSB (right column Table 9).
- The two CMSB articles were co-publications written by authors from several institutes within the CMSB: i.e. Leiden University Medical Center (LUMC), TNO and Erasmus Medical Center (EMC) for (Henneman, Schaap et al. 2007) and LUMC and TNO for (Kreeft, Moen et al. 2005).
- Three of the WCFS articles were co-publications from stakeholders that were members of the WCFS (Wang, Mariman et al. 2004; Roorda, Hesselink et al. 2005; Rodenburg, Bovee-Oudenhoven et al. 2007).

Additional scientific publications of the DNC were in the form of abstracts, posters, oral presentations, book chapters and dissertations (Hessing 2007; www.nutrigenomicsconsortium.nl 2007)

The scientific articles have been published in nutrition-oriented journals like Nutrition, Nutrition & Metabolism, and in highly specialised journals such as Diabetologica and Atherosclerosis. A contribution was made to Nature Review Genetics[42]. The articles also encompassed introductions on issues (van Ommen 2004), reviews (Corthésy-Theulaz, Dunnen et al. 2005; Afman and Müller 2006) and opinions (Müller and Kersten 2003). The content of the scientific articles reflects the findings of the DNC. The scientific articles reported on gene-gene and gene-nutrient interactions

42 The first dedicated nutrigenomics journals like the Journal of Nutrigenetics and Nutrigenomics (first issue November 2007) only appeared after the DNC ended in 2007.

**Table 9** DNC scientific articles

| DNC scientific articles (co-)authored by | | |
|---|---|---|
| **WCFS** | **CMSB** | **WCFS&CMSB** |
| **co-publications** | **co-publications** | **co-publications** |
| (Wang, Mariman et al. 2004)<br>(Roorda, Hesselink et al. 2005)<br>(Rodenburg, Bovee-Oudenhoven et al. 2007) | (Henneman, Schaap et al. 2007)<br>(Kreeft, Moen et al. 2005) | (Corthésy-Theulaz, Dunnen et al. 2005) |
| **Publications by one stakeholder of the WCFS:** | | |
| (Aarts, Schrauwen et al. 2005)<br>(Afman and Müller 2006)<br>(Hoeks, Hesselink et al. 2006)<br>(Kaput, Ordovas et al. 2005)<br>(Mandard, Zandbergen et al. 2006)<br>(Mariman 2006)<br>(Müller and Kersten 2003)<br>(Patsouris, Reddy et al. 2006)<br>(Schrauwen, Hoeks et al. 2006)<br>(van Ommen 2004) | | |

and on tools for nutrigenomics research that were and can be used for nutrigenomics research. Examples of gene-gene and gene-nutrient interactions studied in the DNC are the influence of plasma apoAV on APOA5 S19W polymorphisms which are associated with variations in serum triglyceride-level and hypertriglyceridemia[43] (Henneman, Schaap et al. 2007); the influence of both genotype and diet on lipid metabolism and inflammation (Kreeft, Moen et al. 2005); and the relation between lipids and insulin resistance (Aarts, Schrauwen et al. 2005; Hoeks, Hesselink et al. 2006; Schrauwen, Hoeks et al. 2006). Tools that have been developed and used are, for example, microarray technology (Kreeft, Moen et al. 2005; Patsouris, Reddy et al. 2006). According to the Dutch Nutrigenomics Consortium the *"major achievements"* were (Hessing 2007):

- Setup and validation of Oracle-based LIMS database Madmax for storage of raw and normalised microarray datasets;
- Microarray analysis of several large mouse and human studies using the improved standardised microarray pipeline with normalisation procedure and quality control;
- Finishing several larger mouse intervention studies including the "Leiden" study with genetically sensitised ApoE3Leiden mice;
- Metabolomics analysis of several large studies (Leiden study, Human Pilot study);
- Identification of several gene polymorphisms associated with the HYPLIP sensitising genotype;
- Improvement of microarray data analysis by combining several bioinformatics and pathway mining programs;
- Employment of the FIAF-transgenic mouse as proof-of-principal mouse model for Nutrigenomics research;

43 High blood levels of triglycerides are related to the Metabolic Syndrome.

- First identification of PPARα as the hepatic sensor for dietary fatty acids and further understanding of the PPARα-dependent transcriptome in liver and intestine;
- Design and production of the NUGO mouse and human Affymetrix oligonucleotide microarray with improved probe sets for 30% of the price of the 2.0 Affymetrix array.

Before the DNC started there was no uniform design for retrieving, processing and storing data. Each field of research (e.g. nutrition or genetics) and even research group could have its own methods or supplier of microarrays. Standardisation was crucial for the combination of complementary knowledge (as for example was also mentioned by Corthésy-Theulaz, Dunnen et al. (2005)). Therefore, the stakeholders within the DNC also focused on the *standardisation* of methods, experiments and databanks for future reference and comparison (interviews 2006-05-10, 2006-06-07). The standards for nutrigenomics research within the DNC were set during meetings between the stakeholders that had to work with the data because it was important for them to be able to work with each other's data. The standards that resulted from these meetings and interactions between the stakeholders solved the problem of non-complementary data. Standardisation in nutrigenomics is also important for product quality and for qualifying health claims for functional foods (interview 2006-05-03(1)).

The science-based research activities within the DNC had not resulted in any patents or patent applications[44]. However, the standardisation process and new microarray technology (two of DNC's "major achievements") are applications that resulted from the DNC research. The stakeholders are also positive about participation in the consortium because it enabled them to increase their (tacit) knowledge: *"we are satisfied with the participation in the WCFS [part of the DNC] because it increased our general knowledge pool"* (interview 2006-08-11). This was also acknowledged by other stakeholders (e.g. interview 2006-09-29). An additional outcome of the cooperation of stakeholders within the DNC is that it allowed the stakeholders to become acquainted with each other, which made it easier for them to contact one another on other issues (interview 2006-08-11), and could lead to new projects (interview 2006-09-29).

### 5.2.2 Realisation of the shared vision

A vision that is shared between heterogeneous stakeholders in an emerging technology binds the network together and acts as a driver for innovation. The shared vision encompasses i) a perceived problem, ii) the goal that the stakeholders want to achieve, iii) the objectives within this goal, and iv) how to achieve these objectives.

The co-construction of the shared vision by the stakeholders was initiated by Unilever around 2002. Unilever perceived the rapid increase in the prevalence of obesity in the Netherlands as a major problem (interview 2006-06-07). During the 1980s

44 The DNC website reported a prize-winning patent (www.nutrigenomicsconsortium.nl/news-05june07.html 5-6-2007). However, this patent was not the result of a DNC project (email conversation with prize winner).

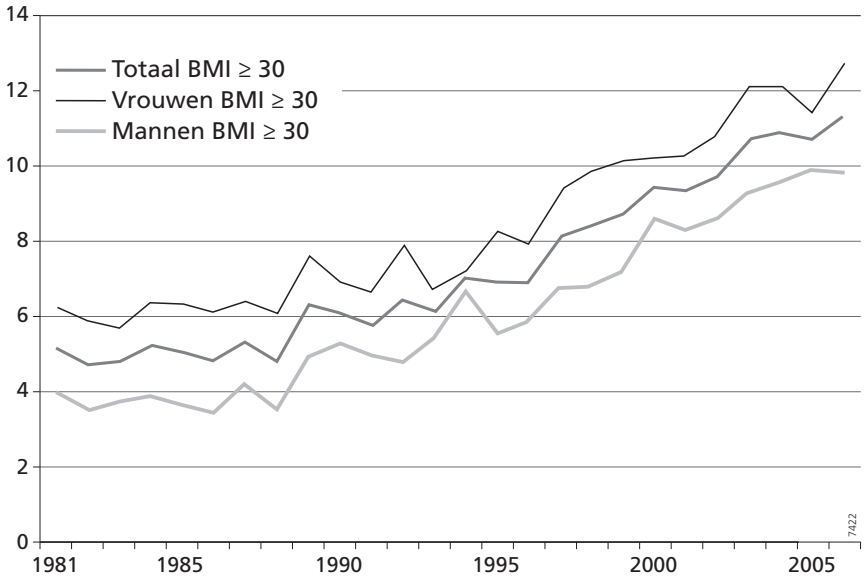


**Figure 24** Obesity in the Netherlands among adults (20+) 1981-2006 (Beuk 20 March 2007)

approximately 6% of Dutch adults were obese (i.e. BMI≥30[45]). Since the 1990s an increase in prevalence was visible, going beyond 10% in 2002 (Figure 24).

In order to address the prevalence of obesity, Unilever envisioned collaboration with heterogeneous stakeholders in research that would contribute to insights into obesity. The DNC stakeholders co-constructed a shared vision during network formation. This DNC shared vision was an 'integration' of the individual stakeholders' visions that were related to the stakeholders' specific knowledge on nutrition or genomics and research techniques (see §5.3.2). The shared vision acted as a driver for nutrigenomics research and innovation within the DNC because it conveyed the overall (innovative) goal of the DNC as propagated by the DNC stakeholders.

Obesity is the starting point of the Metabolic Syndrome[46]. *"According to the American definition of the Metabolic Syndrome, Cardio Vascular Diseases are the end point of the Metabolic Syndrome. Before the Metabolic Syndrome, there is chronic metabolic stress (indicated by e.g. disturbed glucose levels). [Metabolic stress] is central in the Nutrigenomics Consortium because a stress situation can be reversed"* (interview 2006-08-18). Because metabolic stress can be reversed, the goal of the DNC became to find solutions for metabolic stress through nutrigenomics research (Figure 25). Accordingly, the goal of the DNC encompassed two objectives: 1) to understand the events during metabolic stress, and 2) to develop novel food products that could be used to possibly prevent or treat metabolic stress. *"(M)etabolic stress describes changes in the plasma and/or cellular concentration of nutrients and metabolites, which might*

45 BMI= (Weight in Kilograms)/((Height in Metres) x (Height in Metres))

46 For more information on the Metabolic Syndrome see §3.3.

## Nutrigenomics Consortium


The Nutrigenomics Consortium aims to increase our understanding of the events unfolding during metabolic stress,with the ultimate objective to discover and validate molecular biomarkers for the early detection of metabolic stress and to identify and develop novel food components for dietary management and prevention of metabolic stress.

**Figure 25** The DNC goal as stated on the NGI's home page (www.genomics.nl 2008)

*lead to the disruption of cellular function (..) metabolic stress is the key to understanding diet-related diseases*" (Müller and Kersten 2003) (Also see Figure 26).

The stakeholders' expertise, the related individual visions, and the integration of these individual visions was also discernible in the approach (i.e. the fourth elements of the shared vision) taken by the DNC to realise its goal and objectives. The research itself was organised in six interrelated work packages and one integrating work package. The work packages of the DNC were (Hessing 2007)[47]:

A. Intestine and metabolic stress – To identify human relevant, gut-derived biomarkers of insulin resistance syndrome (IRS)[48], by using dietary stressed mouse models and "omics" technologies[49]. (WP leader: NIZO Food Research)
B. Liver and metabolic stress – To understand fatty-acid-dependent gene regulation in the liver and to identify human-relevant, liver-derived biomarkers of insulin resistance syndrome, with a focus on the interactions between nutrient and pro-inflammatory signalling (a so-called two-hit model). (WP leader: Wageningen University, Section Human Nutrition)
C. Peripheral tissues & metabolic stress – To develop and validate molecular signatures of muscle and adipose tissue to predict dietary responsiveness at the individual level. (WP leader: University Maastricht, Human Biology, NUTRIM)
D. Susceptibility genes & metabolic stress – To identify genes and metabolic pathways contributing to early signs of metabolic syndrome by means of QTL[50] mapping in man and mouse. (WP leader: Leiden University Medical Centre, Human Genetics)
E. Diet & metabolic stress: Human studies – To demonstrate the feasibility of human nutrigenomics, and to develop and validate molecular signatures to predict dietary responsiveness at the individual level in humans. (WP leader: University Maastricht, Human Biology, NUTRIM)
F. Data management and Systems biology – To provide (guidance in the) analysis of transcriptome data, perform metabolomics analysis and apply statistical evaluation

47 Also see Figure 28, p.106.

48 IRS is ananother name for the Metabolic Syndrome (also see §3.3)

49 See §3.2 for an introduction on "omics" technologies.

50 Quantitative Trait Locus mapping: the statistical mapping of the genotype related to a specific phenotype.

Box 1 | **Detecting the two hits: pro-inflammatory and metabolic stress**

Cells are regularly exposed to stress, which mainly consists of inflammatory stress and metabolic stress. Inflammatory stress is exerted by cytokines that are released in large quantities by immune cells in response to invading microorganisms. Cytokines such as tumour necrosis factor-α (TNF), interleukin-1β (IL-1β) and IL-6 induce the hepatic ACUTE-PHASE RESPONSE which consists of local and systemic reactions and is accompanied by upregulated or downregulated synthesis and/or activation of liver-enriched transcription factors[68–71]. Cytokines promote the synthesis of acute-phase proteins, in part by downregulating nuclear receptors, such as peroxisome proliferator-activated receptor-α (PPARα), which suppress the expression of genes encoding acute-phase proteins such as serum amyloid protein and C-reactive protein[37,72]. However, this inflammatory response is a double-edged sword, particularly if it is chronic. Pro-inflammatory cytokines can induce cytotoxicity that, in the worse-case scenario, can lead to liver failure[68,73].

Pro-inflammatory stress is directly linked to an immune response, whereas metabolic stress describes changes in the plasma and/or cellular concentration of nutrients and metabolites, which might lead to the disruption of cellular function. One important group of compounds that cause metabolic stress are lipids, or more specifically fatty acids. In healthy individuals, the negative-feedback system that is mediated by PPARs acting as nutrient sensors (see discussion in the main text) can deal with fluctuations in free fatty-acid levels in the plasma (panel a). However, in individuals with conditions such as diabetes and obesity that cause permanently elevated plasma levels of free fatty acids (metabolic stress; 'hit one'), who then, as part of an immune response, have cytokine-induced downregulation of PPARα and other nuclear receptors (pro-inflammatory stress; 'hit two'), the system is overtaxed (panel b). In this case, fatty acids accumulate as triglycerides and spill over into harmful pathways. If triglycerides accumulate in non-adipose tissues, the individual's sensitivity to proinflammatory stress will increase further and might lead to significant organ dysfunction. For example, a combination of excess fat storage and inflammatory stress in the liver can ultimately result in cirrhosis[74].

We are convinced that the interaction between pro-inflammatory stress and metabolic stress is the key to understanding diet-related diseases. Although some might disagree with this view, the role of inflammatory processes in diseases such as atherosclerosis, insulin resistance and cirrhosis is widely recognized[75–78]. So, we believe that understanding how the 'two hits' interact is essential for the application of nutrigenomics in disease prevention.

In future, nutrigenomics tools should allow the collection of 'healthy' diet-related expression signatures as appropriate baseline data (panel a). By comparing these signatures with 'stress' signatures (panel b) that are derived from nutrigenomics experiments, we might be able to identify early molecular biomarkers for individuals with sensitive genotypes under sustained metabolic and pro-inflammatory stress that could lead to serious conditions such as cirrhosis or insulin resistance. With enough early warning, dietary intervention might reverse this process, regain homeostatic control and prevent these conditions in at-risk groups. Microarray panels reproduced with permission from REF. 46 © (2003) National Academy of Sciences.

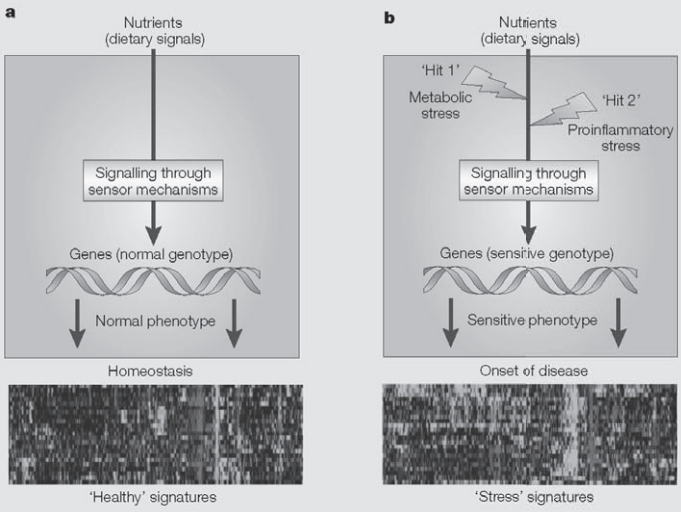


**Figure 26** Metabolic stress and nutrigenomics (Müller and Kersten 2003)

on all relevant studies of the Consortium in order to integrate the results to a "systems" level. (WP leader: TNO Quality of Life, Zeist)

I. (Integrating WP) To coordinate large nutrigenomics studies by applying the NGC data analysis pipeline and to improve Nutrigenomics data handling and storage. (WP leader: Wageningen University, Section Human Nutrition)

The work packages corresponded with the expertise of the stakeholder that had the lead in the relevant work package. For example, TNO had expertise in the study of complex-complex interactions, which are common in nutrition research, based on their expertise in pattern recognition (interview 2006-08-17). TNO could employ this expertise in WP F.

To summarise: the shared vision was co-constructed as follows at the beginning of the DNC in 2003: The perceived problem was the prevalence of obesity, and in order to address this problem the DNC set itself the goal of finding a solution for this increasing health problem. Therefore, two objectives were set: 1) to understand metabolic stress, and 2) to develop food products that would prevent metabolic stress. The approach taken to reach the goal and objectives of the DNC was organised in work packages. The extent to which this shared vision could be realised by the DNC stakeholders would only become known at the end of the interactive learning process within the DNC in 2007. During the DNC's existence the prevalence of obesity remained a considerable health care problem as illustrated in Figure 24. In order to reach the goal all the work packages were carried out. However, eventually only the first objective of the shared vision could be realised by the stakeholders: to gain a scientific understanding of the factors involved in metabolic stress. In 2007, there were no applications as yet based on these new insights. In § 5.3 we further analyse how the co-construction and realisation of the shared vision were influenced by the interactive learning process between the stakeholders within the DNC.

### 5.2.3 Summarising the interactive learning outcome

Table 10 provides an overview of the interactive learning outcome of the DNC. The interactive scientific knowledge outcome of the DNC was covered in scientific articles (publications and co-publications) that reported on gene-gene and gene-nutrition interactions, and tools for nutrigenomics research. Of the *"major achievements"* of the DNC, the standardisation process of research methods was the result of the tacit knowledge exchange between the stakeholders. The standards are the codification of the interactions between the stakeholders regarding the exchange of data. This standardisation solved the problem of data being incompatible and incomparable. Furthermore, new microarrays were developed that were used for nutrigenomics research and the stakeholders increased their (tacit) knowledge pool (e.g. know-how and expertise on data storage and retrieval, which solved the problem of incompatible and incomparable data).

We described the shared vision that was co-constructed at the beginning of the DNC in 2003 and the extent to which this shared vision was realised by the stakeholders at the end in 2007. The prevalence of obesity in the Netherlands was perceived as a major health care problem and the goal of the DNC became to find a solution for this problem. Therefore, two objectives were formulated: 1) to gain insight

**Table 10** Summary of interactive learning outcome of the DNC (highlighted in bold)

| | **DNC** |
|---|---|
| Interactive scientific knowledge outcome | • 10 publications, 1 WCFS/CMSB co-publication, 3 WCFS co-publications, 2 CMSB co-publications<br>• no patent application<br>• standardisation<br>• increase in know-how, expertise, and problem-solving capabilities |
| Realisation of shared vision | • perceived problem: obesity<br>• common goal: to understand processes underlying MS and find a treatment<br>• objectives:<br>1) to increase understanding of the events unfolding during metabolic stress and<br>*2) develop novel food components [not realised]*<br>• Approach: 6 interrelated work packages and 1 integrative work package |

into metabolic stress factors and 2) to develop foods for the treatment and prevention of metabolic stress. The approach taken to achieve the goal and objective of the DNC was organised in six interrelated work packages and one integrating work package. In 2007 all work packages had been carried out, but the stakeholders were only able to realise the first objective of the shared vision.

## 5.3 Interactive learning process in the DNC

In this section we turn to the second sub-question in the analytical framework for the case studies:

7. *How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process?*

The answer to this question gives insight into the interactive learning process and how it influenced the co-construction and realisation of the shared vision and also the interactive scientific knowledge outcome. The elements of the interactive learning process are the *prime mover, network formation, intermediary and knowledge flows*. The prime mover is the first stakeholder within an emerging technology that undertakes an observable action based on a sense of urgency and mutual dependency (on knowledge and resources) that can lead to a collaboration of complementary stakeholders. The *network formation* of a consortium like the DNC is indicated by an increase in interacting stakeholders, linkages and contact moments between them. The intermediary acts as 'translator' between complementary stakeholders who are unable to absorb knowledge directly from each other because they have different expertise and are not familiar with each other's knowledge pool (e.g. nutrition versus genomics). The *knowledge flows* contain the knowledge that is exchanged between the stakeholders.

We start with a description of the influence of the interactive learning process on the interactive scientific knowledge outcome (§5.3.1). We then focus on the influence of the interactive learning process on the co-construction and realisation of the shared vision (§5.3.2). The findings are summarised in §5.3.3.

### 5.3.1 Interactive learning process and interactive scientific knowledge outcome

The network formation of the DNC was started by Unilever. Around 2002 the Dutch-based multinational Unilever identified three trends (interview 2006-06-07):

1. An increasing prevalence of obesity;
2. An aging population; and
3. An increase in health awareness among consumers.

In the perception of Unilever these trends were rather urgent and might possibly be addressed with nutrigenomics research. For Unilever, nutrigenomics research could create future market opportunities in the form of functional foods. At the same time Unilever was aware of a mutual dependency regarding complementary knowledge and resources (e.g. research funds and facilities). Unilever was a food company with experience in nutrition research, but nutrigenomics research would be dependent on a combination of complementary knowledge from nutrition and genomics. According to Unilever (interview 2006-06-07), nutrigenomics research would be costly and take a long period of time to carry out. In order to combine resources and complementary knowledge, Unilever started to contact other stakeholders and form a network around nutrigenomics research.

Around 2002, the Wageningen Centre for Food Sciences (WCFS) was approached by Unilever. The possibilities for the construction of a nutrigenomics research strand within the WCFS were explored. Unilever was a member of the WCFS and highly satisfied with the collaboration with other organisations in the WCFS. Therefore, Unilever wished to embed the nutrigenomics research in the WCFS (interview 2006-06-28). Unilever requested the director of the WCFS to take the lead in the construction of the nutrigenomics research programme (interview 2006-06-28). As the name indicates, the Wageningen Centre for Food Sciences was specialised in nutrition research, but nutrigenomics research encompasses nutrition and genomics research. Therefore, cooperation with a complementary organisation was sought. At this stage the Centre for Medical Systems Biology (CMSB) was contacted. The CMSB was specialised in genetics[51] and was also familiar with the Metabolic Syndrome (interview 2006-10-17). Before the CMSB was contacted for collaboration with the WCFS in nutrigenomics research, the CMBS itself had investigated the possibilities for collaboration in genomics research in the light of recent discoveries (e.g. the results from the Human Genome Project[52]) (interview 2006-10-17). Collaboration with other stakeholders in genomics research was expected to lead to synergies between genomics research institutes because *"genomics is boundary-crossing and interdisciplinary, which makes the combination of competences desirable"* (interview 2006-10-17). These possibilities to collaborate in genomics research had been investigated prior to the establishment of the CMSB in 2003 and had resulted in 2001/2002 in a so-called 'blue book' that described the possibilities and synergies for collaboration in genomics

51 As we explained in §3.2 there is a 'technical' difference between genetics and genomics, which is blurred in the daily usage of these terms. We use the term nutrigenomics for all research into the relation between genomes, nutrition and disease (risk) and the future applications that might result from this research.

52 The director of the CMSB had been the president of the Human Genome Project in 1998/1999

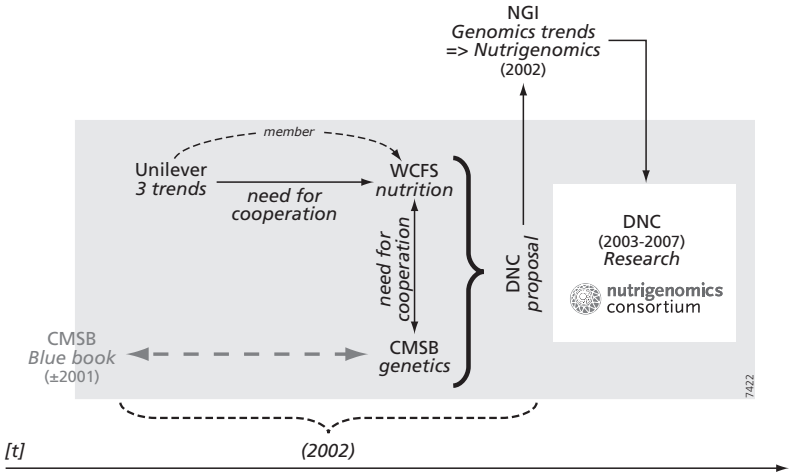


**Figure 27** Network formation of the Dutch Nutrigenomics Consortium

research. The blue book had an explorative character and was also intended to be used when funding opportunities became available (interview 2006-10-17). When the CMSB was contacted by the WCFS for the formation of the Dutch Nutrigenomics Consortium, the CMSB blue book was used as input. Together, the Wageningen Centre for Food Sciences (WCFS) and the Centre for Medical Systems Biology (CMSB) applied for a grant to form the Dutch Nutrigenomics Consortium at the NGI. The network formation of the DNC is visualised in Figure 27.

Nutrigenomics research is a collaborative effort of heterogeneous stakeholders that have to combine i) scientific knowledge from nutrition and genomics, and ii) specific research techniques (see e.g. (Van der Werf, Schuren et al. 2001)). In order to combine complementary knowledge and research techniques, the DNC was organised in interrelated work packages (Figure 28). For each work package one stakeholder had the lead, and different organisations could cooperate within one work package (interview 2006-08-11). Six of the seven work packages were led by a WCFS stakeholder; WP D was headed by a CMSB organisation. The cooperation of multiple stakeholders within a work package resulted in co-publications by these stakeholders (Table 9). The knowledge flows between the stakeholders within the work packages resulted in scientific articles. Since most work packages were headed by WCFS stakeholders, most publications are 'WCFS' articles. The WCFS organisation produced three co-publications and the CMSB organisation one. Interactive learning between the WCFS and CMSB is indicated by the resulting co-publication (i.e. (Corthésy-Theulaz, Dunnen et al. 2005)). An explanation why only one of the articles is a co-publication of WCFS and CMSB stakeholders is that not all organisations interacted (personal communication with researcher, interview 2006-05-03). Of the CMSB stakeholders only the LUMC and TNO interacted with the WCFS (interview 2006-07-04). *"The CMSB contains a lot of valuable knowledge, but they operate more independently than the other organisations in the DNC"* (interview 2006-08-18). In order to facilitate the exchange of data and knowledge between the stakeholders, standardisation (WP I) was

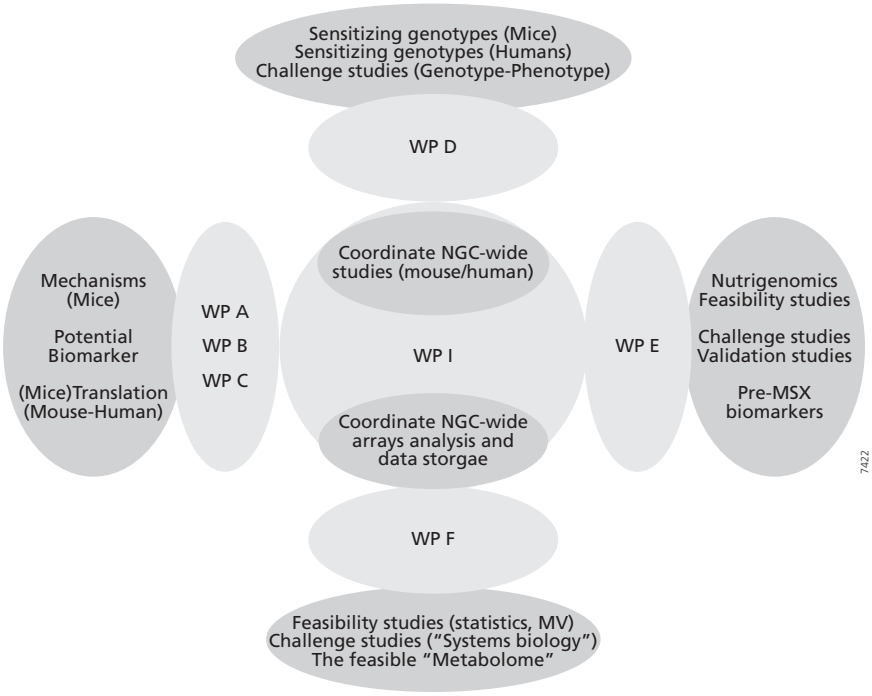


**Figure 28** DNC 7 work packages (Hessing 2007).

an important aspect of the interactive learning process within the DNC (interviews 2006-5-10 and 2006-6-7).

Different 'translations' of knowledge by *intermediaries* were perceptible in the DNC. First, the research performed within the WCFS was science based. So-called "exemplification projects" were organised in order to explore the possible future application of the resulting scientific knowledge (interviews 2006-07-10, 2006-08-11, 2006-09-29). In these exemplification projects TNO acted as an intermediary between the research institutes and companies within the DNC. Fundamental knowledge was translated in the exemplification projects into examples that could be further developed by various stakeholders into future applications (interview 2006-08-29). The exemplification projects can be seen as virtual future scenarios without the production of real applications (e.g. food components). Second, for the scientific research, mouse and human genetics models (WP D) were used, both of which were familiar to nutritional scientists (at WCFS) and genetics scientists (at CMSB). Using and interpreting these models was essentially the same: *"100 arrays of mice or humans with rheumatism does not really make a difference"* (interview 2006-10-17). Therefore, the human and mouse models enabled stakeholders to discuss and exchange knowledge from a mutual starting point. As such, these objects could be regarded as *intermediaries* that facilitate the knowledge flows between nutrition and genomics stakeholders.

*To summarise:* prime mover Unilever identified new possibilities for the prevention and treatment of obesity and possible new functional foods through nutrigenomics research. Unilever acknowledged a mutual dependency with complementary stakeholders for knowledge and resources. To this end, Unilever contacted the WCFS. Hereafter the CMSB was contacted for its complementary knowledge on genetics. Research within the DNC was organised in work packages. The research resulted in tacit knowledge exchange and publications. During the research, intermediaries helped to cross boundaries between the knowledge pools of the complementary stakeholders.

### 5.3.2 Interactive learning process and realisation of the shared vision

In 2003 the DNC started with the following co-constructed shared vision: the increase of obesity was the major perceived problem and the goal of the DNC stakeholders was to start providing a solution to this problem. To do this, two objectives were formulated, namely to increase insight into metabolic stress (which is related to obesity), and to develop novel food components. In order to reach these objectives the approach of the DNC was arranged in work packages. Through the research in the period 2003-2007 it would become clear to what extent the stakeholders could realise the *shared vision*.

The *shared vision* at the beginning of the Dutch Nutrigenomics Consortium in 2003 was the result of an 'attuning process' between the mission at Dutch governmental level regarding the knowledge infrastructure and the co-construction of a shared vision within the Dutch Nutrigenomics Consortium (Figure 29). The general mission at the governmental level of the Dutch Cabinet was for the Netherlands to have a "*pioneering role in the 'Europe of knowledge and innovation'*" (Tijdelijke Adviescommissie Kennisinfrastructuur Genomics 2001). This general mission was not targeted towards a specific subject or (emerging) technology; it was an overarching mission that could be used as guidance for all innovative activities that contribute to the role of the Netherlands in Europe. In line with the Dutch Cabinet's general mission, the Temporary Advisory Committee Knowledge Infrastructure Genomics formulated a more concrete advice for the "*reinforcement of the genomics knowledge infrastructure*" (Tijdelijke Adviescommissie Kennisinfrastructuur Genomics 2001) through the establishment of a national coordinating body, the Netherlands Genomics Initiative (NGI). At the network level, *prime mover* Unilever envisioned collaboration between heterogeneous stakeholders in which basic research could be performed that would be required to match the identified trends and possibilities of nutrigenomics. During the *network formation* the WCFS and CMSB presented the first proposal for the DNC to the NGI in order to acquire funding. This first proposal was rejected by the NGI because it was too versatile, or as one interviewee stated *"all the hobbies of the researchers were present"* (interview 2006-5-3-(1)).

Before presenting the second proposal to the NGI a brainstorm session was organised with the help of an external facilitator acting as an intermediary. Thanks to this session the stakeholders co-constructed a shared vision that was a 'integration' of the stakeholders' individual visions. The stakeholders' individual visions were related to their specific knowledge on nutrition or genomics and research techniques. A combination of these expertises was needed to address metabolic stress. These

expertises could be integrated through the interrelated work packages, each of which was headed by one stakeholder whose expertise corresponded with the work package topic. The work packages were integrated in a so-called integrating work package that entailed the consortium-wide coordination of mouse/human studies and the standardisation of data. The work packages had a twofold purpose: 1) to pursue the individual visions of the stakeholders in the work packages in which they had the lead through collaboration with other stakeholders within that work package, and 2) to contribute to the overarching shared vision through the integrating work package.

The resulting streamlined proposal was granted funding through the NGI. From this point on the DNC's goal was communicated through e.g. the NGI's website: *"The Nutrigenomics Consortium aims to increase our understanding of the events unfolding during metabolic stress, with the ultimate objective to discover and validate molecular biomarkers for the early detection of metabolic stress and to identify and develop novel food components for dietary management and prevention of metabolic stress."*(www.genomics.nl 2008). While one shared vision of the DNC was communicated to the outside world through e.g. www.genomics.nl and PR material, tacit individual visions co-existed within the DNC. These individual visions were related to the differences in expertise resulting from the heterogeneous stakeholders' different backgrounds. For example, the focus of Unilever was margarine, whereas Campina was committed to butter (interview 2006-08-29). However, these individual differences did not deviate from the general shared DNC vision of finding a solution to metabolic stress and the development of novel food components. Only the envisioned application of novel food components in e.g. butter or margarine might differ. Not all stakeholders were confident about the development of applications: *"Nutrigenomics is not a short-term issue and at first I didn't even think of concrete products"* (interview 2006-08-11). Others were confident that the research within the DNC would yield tools that could be used in various fields (interview 2007-06-10).

The increase in obesity continued during the existence of the DNC (2003-2007). This is also visible in Figure 24. The goal of the DNC to contribute to a solution for the increasing problem of obesity remained intact. In order to reach this goal the planned work packages were carried out. Research within the work packages resulted in knowledge flows between the stakeholders, an accumulation of knowledge, and scientific articles (Table 9). Through their research the stakeholders found that i) nutrigenomics was far more complex than thought during the formation of the DNC in 2003, and ii) more research would be needed to gain sufficient insight into the factors involved in metabolic stress before novel food components could be identified (interviews 2006-05-10, 2006-06-07, 2006-7-10, 2006-8-18). *"When we started with nutrigenomics we had a more positive view than now. We underestimated [the complexity]"* (interview 2006-07-10). This can also be illustrated with a statement in one of the scientific articles:

*"Although the degree of saturation seems to be related to the development of insulin resistance in animals (saturated fatty acids increase insulin resistance, whereas unsaturated fatty acids – especially omega-3 fatty acids from fish oil – reduce insulin resistance), this has not been replicated in human intervention studies. Therefore,* ***more***

***well-controlled human intervention studies are needed*** *to elucidate the role of total fat intake and dietary fatty acid composition on the development of insulin resistance.*" (Aarts, Schrauwen et al. 2005) (bold print by RV)

Thus, the scientific insights the stakeholders had gained through the research within the DNC made it evident that nutrigenomics research was more complex than originally thought, and more research would be necessary before novel food ingredients could be designed. Due to these insights, the stakeholders put more emphasis on the unfolding of metabolic stress factors, making the search for solutions for the metabolic stress and the development of novel food components of indirect importance. Consequently, at the end of the DNC, in 2007, the stakeholders had only realised the first objective within the shared vision; to gain insight into the factors involved in metabolic stress.

To summarise: prime mover Unilever had a vision about the contribution of nutrigenomics research to prevent and treat obesity. During the network formation a shared vision was co-constructed by the DNC stakeholders. The co-construction of the DNC shared vision was the result of an integration of the individual visions with the help of an intermediary. The individual visions were based on the stakeholders' expertises; these different expertises of the stakeholders were also reflected in the work packages they headed. Research performed within the work packages and the combination of the resulting knowledge showed that nutrigenomics research and the uncovering of factors involved with metabolic stress was highly complex. Consequently, more research would be needed before novel food components could



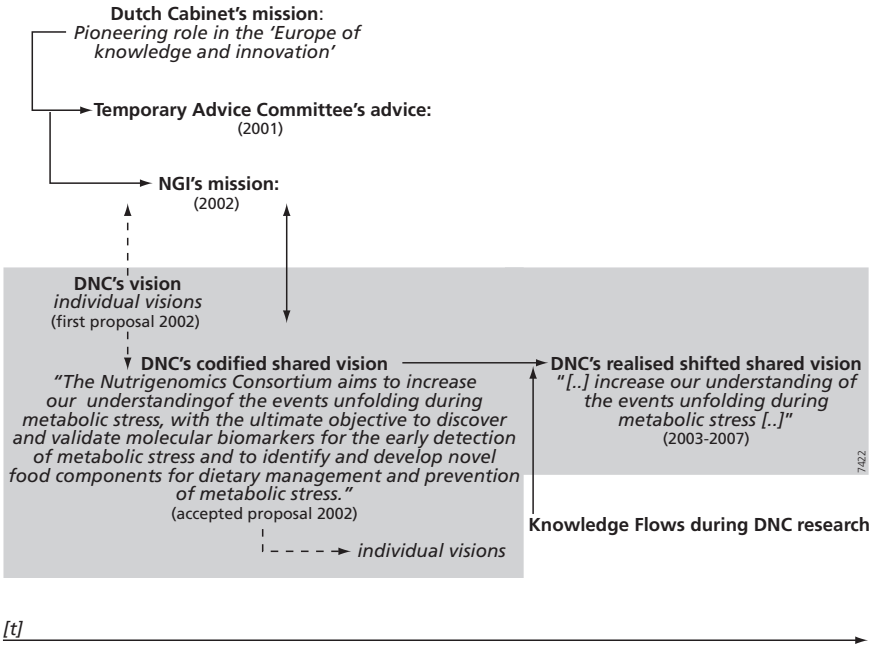


**Figure 29** Co-construction and realisation of shared vision of DNC

be designed. The stakeholders focused on unravelling the metabolic stress factors and at the end of the DNC the stakeholders had only realised part of the shared vision, namely to understand metabolic stress (i.e. the first objective of the DNC).

### 5.3.3 Summarising the interactive learning process and interactive learning outcome

Unilever was the *prime mover* that started the formation of the DNC. The prevalence of obesity created a sense of urgency for Unilever: Nutrigenomics research could provide insight into obesity, and the scientific knowledge could be used for future functional foods. Because knowledge from nutrition and genomics research had to be combined, Unilever was aware of the mutual dependency between the stakeholders within these two fields of knowledge. Therefore Unilever first contacted the WCFS (with know-how and expertise in nutrition research). Later, the director of WCFS contacted the CMSB (genomics) for the *formation of a network*. The *knowledge flows* between the stakeholders within the work packages accumulated into an increase in tacit knowledge and co-publications. An important result of the interactive learning process within the DNC is the standardisation of research and data which facilitated the interchange of research data and made data accessible for future reference. Several *intermediaries* were visible, translating knowledge within the DNC. Sometimes, the intermediary can be attributed to a single stakeholder (e.g. TNO in the exemplification projects). An intermediary merged the individual visions of the stakeholders to form the shared vision of the DNC. Also intermediary 'objects' (i.e. mouse models) were visible.

By 2007 the perceived problem and envisioned goal of the DNC were still the same as at the beginning of the DNC in 2003. All work packages had been carried out in the meanwhile. The resulting scientific insight showed that nutrigenomics research was particularly complex and many scientific questions still had to be answered. Consequently, the stakeholders only realised the first objective of the shared vision: "*… understanding of the events unfolding during metabolic stress*" (www.genomics.nl 2008). Although the understanding of metabolic stress increased, more knowledge would be needed for the development of novel food components (second objective).

## 5.4 Conditions for interactive learning in the DNC

In the previous section we described how the elements of the interactive learning process (i.e. the prime mover, network formation, knowledge flows and the intermediary) influenced the interactive learning outcome (i.e. interactive scientific knowledge outcome and the realisation of the shared vision). In this section we describe how the conditions for interactive learning (i.e. geographical, cognitive, regulatory, cultural, social and organisational proximity) influenced the interactive learning process. Therefore we turn to the third sub-question of the analytical framework:

8. *How were the elements of the interactive learning process influenced by the conditions for interactive learning?*

We start with geographical proximity, followed by cognitive, regulatory, cultural, social, and organisational proximity (§5.4.1- 5.4.6). We give a short description of each condition[53] before describing its influence on the prime mover, network formation, knowledge flows and intermediary. We summarise our findings in §5.4.7.

### 5.4.1 Geographical proximity

*Geographical proximity* facilitates face-to-face interaction (Feldman 1994; Gertler 2003), which enables *tacit* and *complex knowledge* flows (Malmberg and Maskell 1999; Doloreux 2004). Therefore, it is expected that *geographical proximity* facilitates the first meetings between stakeholders in which tacit and complex knowledge is exchanged. Since the exchange of tacit knowledge is also important during the actual research it is assumed that the prime mover searches for complementary stakeholders in his immediate vicinity. Geographical proximity is indicated by an agglomeration of stakeholders in a geographical unit (i.e. the same region).

The DNC stakeholders were located in the Netherlands, with centres of gravity in the Wageningen Food Valley (WCFS) and Leiden (CMSB). Besides the formal and administrative 'headquarters' of the DNC (i.e. WCFS), other non-DNC 'food' organisations were also located in this Valley[54]. This convenient co-location of food organisations was one of the reasons for Campina to centralise and relocate its research institutes that were scattered all over the world: "*The clustering of Campina's worldwide R&D activities in Wageningen is a well deliberated decision: The location in the Food Valley – were the WUR is located – makes nearby knowledge as well as scientific instruments at the university easily accessible*" (interview 2006-09-29).

Unilever started the formation of the DNC realising that collaboration with complementary stakeholders was a necessary condition for nutrigenomics innovations. Therefore, Unilever first contacted the WCFS for collaboration in nutrigenomics research. The collaboration was expanded with the CMSB for complementarities at the genetics spectrum of nutrigenomics research. Together, these organisations formed the DNC (see Figure 23). It was very convenient for the *network formation* of the DNC that all stakeholders were located in the Netherlands because it made meeting each other easier. Complicated and sensitive subjects could be discussed at these meetings. One example of this were the meetings that were needed to arrive at a mutual agreement on Intellectual Property Rights (IPR) (interview 2006-10-17). (We further elaborate on the IPR issues in §5.4.3.)

Numerous formal and informal face-to-face meetings were held in which tacit and complex knowledge was interchanged. Within the work packages researchers not only met regularly during formal meetings, but also had informal contact, depending on the researchers' needs and wishes (interview 2006-06-28). For example, researchers might exchange research findings, discuss interesting scientific articles or research designs. These meetings had a positive effect on the tacit and complex *knowledge flows*

53 For an elaborate theoretical exploration of the concepts see §2.4.

54 E.g. Aviko, Cargill, Danone, Deli-XL/Ahold, Grolsch Breweries, Heinz, Isotron, Keygene N.V., and Nestlé (www.foodvalley.nl/Paginas/Food%20Valley%20Society.aspx 20-11-2008).

within the DNC. These informal meetings between researchers within work packages were held approximately once every two months for 3-4 hours (interview 2006-05-03). At the overall management level, various formal meetings were used to keep informed about each other's progress (interview 2006-06-28):

- The NGI had 2 meetings with DNC each year to evaluate progress;
- The WCFS[55] board (at CEO level) met 2-3 times a year (interview 2006-08-11);
- The WCFS focal points council met for one day 4 times a year;
- The WCFS programme council convened a 2-day strategy session a year; and
- The WCFS itself made several site visits a year in order to monitor project process (programme directors visiting individual stakeholders).

To summarise: the DNC stakeholders were all located in the Netherlands. For the *prime mover* and during the *network formation,* this agglomeration facilitated the face-to-face meetings during which agreements were settled about IPR issues and future scientific research. During the actual research period frequent meetings took place, at which complex and tacit *knowledge* was exchanged between the stakeholders.

### 5.4.2 Cognitive proximity

*Cognitive distance* enables stakeholders to learn from each other (Boschma 2005), but in order to incorporate external knowledge into one's own knowledge system the cognitive distance should not be too great (Boschma and Lambooy 1999). A common knowledge base is often identified on the basis of the stakeholders' *technological focus, co-citations* and *cross-citations,* and the *journals* stakeholders publish in. A *cognitive distance* between stakeholders creates the potential for learning; it results in the exchange and incorporation of new knowledge. It is expected that a prime mover will search for complementary stakeholders based on the prime mover's own knowledge and desired complementary knowledge. However, a network will only be formed if the complementary stakeholders are convinced that they will be able to bridge the knowledge gap between their complementary knowledge fields. Within this network an intermediary could act as a translator between stakeholders who are unable to learn directly from each other.

The DNC was a collaboration of the WCFS and CMSB. These two organisations had different *technological foci*: the WCFS had expertise in nutrition research and the CMSB in genetics research. Therefore, there is a *cognitive distance* between the stakeholders by virtue of their nutritional or genetics background. This distance is further substantiated by the limited number of co-citations and the absence of cross-citations between the WCFS and CMSB articles. The 16 DNC scientific articles (see Table 9) contain 648 references. The articles produced by the WCFS and CMBS only share two co-citations (circled in Figure 30). The WCFS/CMSB co-authored article (Corthésy-Theulaz, Dunnen et al. 2005) contains some co-citations with articles from the WCFS and CMSB. There were no cross-citations between WCFS and CMSB articles. Also the *journals* in which organisations publish are an indicator for cognitive proximity. Only two articles were published in the same journal: Henneman, Schaap et al. (2007) and Kreeft, Moen et al. (2005) were published in Atherosclerosis. These two

55 The WCFS was the administrative head quarters of the DNC.

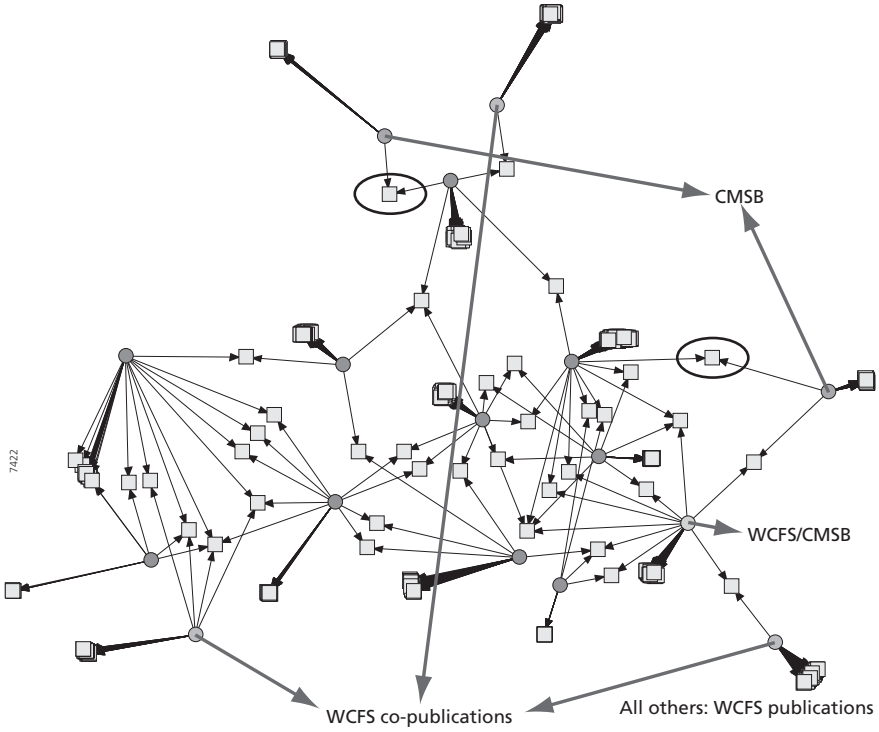


**Figure 30** Co-citation analyses of DNC articles with Usenet6 based on DNC scientific articles (●=article, ■= citations)

articles were both co-publications of stakeholders within the CMSB and featured two authors that were the co-authors of both articles. Thus, regarding the technological focus of the stakeholders, the limited number of co-citations, the absence of cross-citations, and the journals the stakeholders published in, there was a cognitive distance between the stakeholders from nutrition and genetics research.

Unilever was a food company that identified new challenges (i.e. increase of obesity) and new possibilities through nutrigenomics. This company realised that the combination of nutrition and genomics expertise would be required in order to innovate. First they contacted the WCFS for its complementary knowledge at the nutrition spectrum, and later on the director of the WCFS approached the CMSB for its complementary knowledge in genetics. Since Unilever was a food company and WCFS research focused on nutrition, the cognitive distance between these stakeholders was relatively small. The cognitive distance between the CMSB and WCFS was greater due to their different technological foci. The WCFS and CMSB formed a network because they thought they could collaborate and learn from each other.

The cognitive distance creates the potential for the stakeholders to learn if they are able to bridge the distance between their knowledge fields (i.e. nutrition and genetics). From the onset of the DNC one of the major goals had been to exchange and bring

knowledge together and make it useful for the stakeholders: *"The Dutch Nutrigenomics Consortium is a communication channel for knowledge exchange and attuning"* (interview 2006-10-17). For the knowledge flows it was important to both bring in one's own knowledge and at the same time appreciate 'outsider' information from other stakeholders with a different background and focus: *"Actors have to both bring in knowledge as well as appreciate each other at an equal level"* (interview 11-8-2006).

It was important to bridge the distance between complementary knowledge fields, or as one interviewee stated: *"it is important to speak each other's language"* (interview 18-8-2006). If this is not directly possible, a translating intermediary might be of help. Objects such as mouse models helped to bridge the knowledge gap between the stakeholders because both the stakeholders with a nutrition and a genetics background were familiar with these mouse models. TNO carried out exemplification projects in which scientific knowledge was translated into possibilities for application. Despite these exemplification projects some companies within the DNC (i.e. Avebe and Cosun) had more difficulties bridging the distance between science and application. These companies were more focused on the 'classical' consumer food market in general – based on their product portfolio – and saw less added value in the long-term nutrigenomics developments. At the time the interviews were held two companies were leaving the consortium. *"This is mainly caused by their switch in focus. Consequently they perform less research in general and therefore the value of participating in the WCFS diminishes"* (interview 2006-06-28).

To summarise: from a cognitive proximity perspective there is a *cognitive distance* between the WCFS and CMSB. Prime mover Unilever first contacted the WCFS, that was specialised in nutrition research. Because nutrigenomics research would also require genetics knowledge and expertise, the WCFS contacted the CMSB, which was specialised in genetics research. According to the interviewees, the researchers were able to learn from one another (as e.g. expressed in the scientific outcome in §5.2.1). *Cognitive distance* facilitated the knowledge flows between the stakeholders. These were further facilitated through the intermediary objects that acted as a mutual starting point and helped bridge the cognitive distance.

### 5.4.3 Regulatory proximity

*Regulatory proximity at the macro level* refers to i) regulations that reduce uncertainty, and ii) government funding. It is expected that stakeholders are influenced by regulations that reduce uncertainty because they produce a return on investment and therefore stimulate the endeavour to undertake risk-bearing and costly long-term research. Furthermore, organisations and research projects that are dependent on substantial research funds are triggered by government funding because it enables research.

The DNC stakeholders in the Netherlands were all subject to the same *regulations* in the food/nutrigenomics innovation system. The Netherlands is a member of the EU and most of today's legislation is directly related to the EU directives. In relation to the food/nutrigenomics innovation system one regulation was important:

- Due to the *Proposal for a regulation of the European Parliament and of the council on nutrition and health claims made on foods (COM (2003) 424)*[56] only functional foods with scientifically-substantiated food and health claims will be allowed onto the EU market after evaluation by the European Food Safety Authority (EFSA).

The EU legislation made it clear that in the near future only hard-claimed functional foods would be allowed on the European market. The production of functional foods was an important activity of Unilever and therefore the EU legislation stimulated prime mover Unilever to explore the possibilities of nutrigenomics given that nutrigenomics research could be used to produce hard claims. Besides creating a protected market space for hard-claimed functional foods, EU legislation also put an extra burden on food companies because they needed to perform scientific research in order to substantiate their claims. Therefore, stakeholders also started to form consortia because it enabled them to reduce the costs of research (interview 2006-09-29). As such, EU legislation influenced the network formation in two ways: by creating a protected market space and by stimulating collaboration in order to be able to perform research and thus make hard claims possible. At the same time, government funding would reduce the investments that had to be made in research. Funding for nutrigenomics research was made available by the Dutch government through the NGI. Funding was an important factor for the formation of the DNC: *"It is important to have knowledge exchange between research groups, critical mass, interaction with industry, funding and a mutual interest"* (interview 2006-08-18). Drawing in funding was a major reason for stakeholders to collaborate because it enabled them to continue their nutrigenomics-related research: *"In order to gain funding for research we have to make ends meet and therefore multiple financial resources are used. This was also the idea for the focus on nutrigenomics: an extra possibility for research funding"* (interview 2006-07-04). According to Unilever, a governmental role in the form of resources was also expected (or even necessary) due to the risk-bearing and expensive character of nutrigenomics research that could lead to market failure (interview 2006-06-07). Collaboration in a consortium not only brought in government funding but also spread the risk over all the stakeholders (interview 2006-09-29). As such, the consortium functioned as a multiplier for research funds: *"we invest € 1 million in the WCFS and retrieve a research programme of € 20 million"* (interview 2006-06-28). Thus, the availability of funding and the foresight that only hard-claimed functional foods would be allowed onto the EU market stimulated network formation: the funding would (partly) reimburse the stakeholder's research expenses. The hard-claimed functional foods that could be developed on the basis of this research would be entering a protected market which would create a competitive advantage.

*Regulatory proximity at the meso level* in the form of contracts (e.g. mutual agreements and Non-Disclosure Agreements (NDAs)) reduces Intellectual Property Rights (IPR), uncertainties related to patents and publications, and encourages *knowledge flows*.

56 NB This proposal was made in 2003 and accepted by the EU council on 12 October 2006. Since then it is known as EU Regulation 1924/2006 (see http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:EN:PDF). At the time of the existence of the DNC the proposal still had to be rectified by all EU member states.

At the network level, the collaboration between the WCFS and CMSB in the DNC was sealed in a *mutual agreement*. This mutual agreement dealt with *IPR issues* related to DNC research and discoveries. Before the WCFS and CMSB joined forces for nutrigenomics research, they each had their own individual patenting mechanisms: within the CMSB a patent would be owned by the stakeholder that made the discovery and filed for the patent. Within the WCFS one stakeholder would apply for the patent and other interested stakeholders would be given a licence. Discussions during the formation of the DNC resulted in a combined arrangement that satisfied both the CMSB and the WCFS (interview 2006-10-17). The solution was found on the basis of the theme covered by the patent: food-related patents fell under the original WCFS arrangement and medical-related patents under the CMSB arrangement. The *IPR arrangements* prevented unwanted spill-overs because it was clear who owned which knowledge and under which conditions others could use that knowledge (e.g. through patents). Unwanted spill-overs were further prevented by the agreement not to conduct similar research simultaneously outside the DNC (interview 2006-06-28). Within the DNC, pre-competitive research was performed by companies that were competitors outside the DNC. Thanks to these 'unwanted spill-over-preventing agreements' stakeholders tended to let their *knowledge flow* more freely.

To summarise: the presence of funding for the risky, long-term scientific nutrigenomics research and the foresight of a future, protected market through the EU regulation, stimulated the prime mover and network formation. At network level the mutual agreement facilitated the knowledge flows between the stakeholders, since the IPR arrangements prevented unwanted spill-overs.

### 5.4.4 Cultural proximity

*Cultural proximity* is related to different underlying incentive structures for science and industry which might induce a reluctance to share knowledge and could block knowledge flows and interactive learning (Dasgupta and David 1994; Frenken and Van Oort 2004). The differences between the foci of universities and companies on publications and patents respectively, might lead to a conflict: If a finding has been published (in a scientific journal) it can no longer be patented because it is impossible to trace the originality of the idea by the patent applicant. At the same time, patent application may take a long time, hindering a well-timed scientific publication.

The DNC was a joint effort of the WCFS and CMSB and consisted of universities, research institutes and companies. "*Universities are especially involved to score on the scientific level: (strategic) knowledge creation, publications and presentations. Industry is more interested in the acquisition of knowledge on the short term that can be used to produce new products. Of course this does not match.*" (interview 2006-07-10). This is also visible in the pursuit of discoveries: "*We want to go towards applications that are interesting for [our company]. Therefore we want to know if something works and what the relation between costs and feasibility is; if it is feasible, but too costly, then – in principle – it is not interesting for a company. Universities want to know how something works and they choose superior technology instead of feasible technology*" (interview 2006-09-29). The main difference between universities and industry within the consortium were their different 'outcome' foci resulting from the different *underlying*

*incentive structures*. Researchers and research groups at universities are assessed on the basis of their peer reviewed publication output. For companies, the transformation of a scientific invention into an application is more important. Companies are therefore focused more on patents and products: *"An academic partner has a different agenda: they want to publish their research. Innovation is a side issue. At companies it is exactly the other way around: it is nice if an innovation can be substantiated by a publication. You have to know what each other's motives are"* (interview 2006-06-07).

Prime mover Unilever started to contact stakeholders that were able to contribute to nutrigenomics research related to obesity. Unilever fist contacted the WCFS because Unilever was part of this network and had earlier experience with collaboration within the network. The organisations that formed the WCFS were research institutes, universities and companies. As such, the WCFS stakeholders were familiar with the difference in the underlying incentive structure and *"over the years WCFS researchers have become aware of applications"* (interview 2006-06-28). The CMBS organisations were all research institutes, but were also familiar with patenting (interview 2006-10-17). Therefore – like the WCFS – the CMSB also had a dual focus on publications and patents. During the network formation the stakeholders made unambiguous arrangements about patenting. It was therefore known which knowledge could and would be used for publications and patents. As such, the stakeholders worked under a combined incentive structure. Advancements in nutrigenomics (and eventually patenting) could only occur through science-based research. Therefore the collaboration itself could be characterised as a predominantly science-driven culture that facilitated the flow of knowledge between the stakeholders.

Within the DNC we observed a difference in 'management culture' between the CMSB and WCFS. CMSB managers interacted more directly and more frequently with researchers: they saw each other on a daily basis and talked about DNC projects during small talk (e.g. at the coffee machine). Within the WCFS the contacts between researchers and managers were more formalised around progress meetings (interview 2006-10-17).

To summarise: within the DNC there was a formal cultural difference between research organisations and companies based on their different underlying incentive structures and outcome foci. However, in practice all stakeholders had a dual outcome focus on publications and – whenever possible – patents. As such there was no real cultural difference.

### 5.4.5 Social proximity

Social proximity (i.e. trust) between stakeholders is important for the exchange of tacit knowledge. Stakeholders have to trust that others will not misuse complementary knowledge for their sole benefit. This is especially important due to the ubiquitous character of tacit knowledge. Tacit knowledge flows more easily in the presence of shared trust (Malmberg and Maskell 1999). Due to the importance of trust, it is expected that the prime mover will evaluate the presence of trust and contact stakeholders he is already familiar with. If stakeholders do not feel they can trust each other during research (e.g. sharing competitive knowledge), they will not start to

collaborate. Therefore, it is expected that trust stimulates network formation. If trust is lacking between the stakeholders, knowledge will not be shared (equally) between them, thereby hampering knowledge flows and innovation.

Unilever first contacted the WCFS in an effort to start a collaboration with complementary stakeholders in the emerging technology of nutrigenomics. Unilever already had experience with the stakeholders in the WCFS from earlier collaborations (interview 2008-02-13). As such, Unilever trusted these stakeholders on the basis of their shared history and that trust influenced Unilever in its choice to seek further collaboration with the WCFS. At a later stage in the network formation the CMSB was contacted for its expertise in genetics. The CMSB members were already familiar with each other but there was no shared history between the WCFS and CMSB. During the early network formation meetings the WCFS and CMSB stakeholders had already assessed whether they thought they could trust each other during collaboration. The fact that the CMBS and WCFS decided to collaborate indicates that the WCFS and CMSB did trust one another. The importance of trust for their research was acknowledged by the DNC stakeholders: *"You have to trust your partners not to misuse your competitive knowledge"* (interview 2006-08-11). In pre-competitive collaboration it also becomes obvious what the focus of companies and their own research is. It could be very sensitive information in the presence of competitors. Therefore, trust is of special importance for companies. Within the entire DNC (i.e. WCFS and CMSB) the stakeholders trusted each other as long as there was no *"sensitive competition between the members"* (email 2008-02-13). Trust would be dominant as long as the research was pre-competitive and no rivalry emerged between the industrial partners. If a rivalry situation did arise, the stakeholders would fall back on the IPR arrangements set out in the mutual agreement (also see §5.4.3) (interview 2008-02-13).

To summarise: the members of the WCFS already knew each other from previous collaborations and therefore already trusted one another. The same applies with regard to the members of the CMSB. During the network formation the stakeholders assessed the presence of trust. The actual collaboration of the WCFS and CMSB in the DNC indicates that the stakeholders trusted each other. The presence of trust facilitated the exchange of knowledge.

### 5.4.6 Organisational proximity

The production and coordination of complex knowledge is determined by *organisational proximity*. Organisational proximity encompasses the *flexibility* that enables individual stakeholders to pursue their knowledge goal and the *coordination* that enables the combination of complementary *knowledge flows* (Boschma 2005).

The DNC was set up as a virtual network because in practice there was no 'dedicated' DNC research lab (interview 2006-05-03(1)). For example, 20 CSM experts participated in WCFS for approximately 10% of their time (interview 2006-08-11). The DNC organised its efforts around topics and *"closely interacting work packages (..) headed by WP leaders, who are responsible for scientific leadership and project management of their WP*" (Hessing 2007). Within the work packages (see §5.2.2 and Figure 28) several stakeholders could participate and WP leaders managed their WP, which

resulted in *flexibility* at the WP level. Flexibility in the WPs facilitated the 'production' of *knowledge*. The *flow* of this knowledge between the complementary stakeholders was coordinated through the DNC. From the beginning, all activities were *coordinated* through the DNC (i.e. WP I) as had been arranged during the network formation. WP I also entailed standardisation that would make data exchange between WPs easier.

To summarise: organisational proximity was arranged (in work packages) during the network formation. This created flexibility and coordination (i.e. WP I) and facilitated the production and exchange of knowledge within the DNC.

### 5.4.7 Summarising the interactive learning conditions and the interactive learning process

The DNC stakeholders were all located in the Netherlands (i.e. *high geographical proximity*) with an agglomeration of WCFS organisations in the Wageningen Food Valley and CMSB stakeholders in Leiden. There was a certain *cognitive distance* between the stakeholders with their different technological foci in nutrition and genetics. The *regulatory proximity* was *high* both on the macro (i.e. by EU regulations and government funding) and meso level (i.e. by mutual agreements). Since the DNC was a collaboration of research institutes, universities and companies there was a *cultural difference*. However, the organisations in the WCFS were already familiar with cooperation between science and industry organisations and the CMBS also had experience with patenting. As such, the stakeholders had a dual outcome focus and a similar underlying incentive structure. Trust (i.e. *social proximity*) among the stakeholders was present, partly based on a shared history and partly on the assessment of trust at the beginning of the collaboration. The *organisational proximity* encompassed both flexibility in the individual WPs as well as coordination over the different WPs through the integrating work package (i.e. WP I).

Prime mover Unilever started to contact complementary stakeholders. The geographical agglomeration of these stakeholders in the Netherlands facilitated face-to-face meetings. First the WCFS – of which Unilever was already a member – was contacted and later the CMSB for its expertise on genetics. As such, the cognitive difference between these two networks influenced the prime mover in his search for complementary stakeholders. The prime mover was already familiar with the WCFS organisations and already trusted them on the basis of their shared history.

The geographical proximity also facilitated the network formation. During face-to-face meetings the stakeholders could discuss important and difficult issues (e.g. IPR arrangements). During these meetings the stakeholders investigated whether they could learn from each other (i.e. bridge the knowledge differences between them) and trust each other during the actual collaboration. EU regulations and government funding stimulated the network formation, while the mutual agreement – that bound the network together and would prevent unwanted spill-overs during the actual research – was drafted during the network formation. The cognitive distance between the stakeholders was a prerequisite for the network formation because complementary knowledge from the fields of nutrition and genetics had to be combined in order to perform nutrigenomics research. Within the whole DNC (i.e. WCFS and CMSB)

the stakeholders trusted each other as long as there would not be any *"sensitive competition between the members"* (email 2008-02-13). Should that be the case, then the stakeholders would fall back on the IPR arrangements at network level. The history of the WCFS stakeholders resulted in the presence of trust that stimulated the stakeholders to form a network and cooperate in the DNC. The agreement also dealt with the organisation of the DNC in flexible interrelated WPs and coordination of the total research.

Intermediary objects like mouse models helped to bridge the knowledge gap between the stakeholders in nutrition and genetics research because they were familiar to both stakeholders with a nutrition or genetics focus.

The knowledge flows were facilitated through the geographical proximity that allowed for face-to-face contact. The difference in knowledge between the stakeholders made the flow of knowledge between them necessary in order to learn and combine knowledge for nutrigenomics. The research itself had been organised in interrelated WPs that allowed for flexibility and coordination of the work. The culture of the stakeholders did not seem to have an influence on the knowledge flows between them. This is probably attributable to the trust and IPR arrangements between them: the stakeholders trusted that knowledge would not be 'misused' for either patents or publications, and that both possibilities would be tuned to each other. Unambiguous arrangements were made about ownership and licensing of the patents at the beginning of the collaboration.

## 5.5 Conclusion and discussion

In this chapter we have explored the Framework for Interactive Learning in Emerging Technologies within the case of the Dutch Nutrigenomics Consortium. Doing so brought us to the second part of the leading research question:

*How can interactive learning in emerging technologies be conceptualised, and* ***how can this conceptualisation provide insights into interactive learning between stakeholders in nutrigenomics?***

In this section we draw conclusions about interactive learning within the DNC and discuss case study findings.

The DNC started with a co-constructed shared vision that comprised a problem perception (i.e. obesity prevalence) and the goal of finding a solution to this health care problem. In order to achieve this goal the DNC had two objectives: i) to unravel the factors involved in metabolic stress, and ii) to develop novel food components for the prevention and treatment of metabolic stress. In order to realise the shared vision the stakeholders set up a research approach around work packages. The research within the DNC resulted in a scientific knowledge outcome, which is reflected in scientific articles, the major achievements of the DNC, and the increase in tacit knowledge. Due

to the scientific insights gained during the consortium period, the stakeholders were able to realise the first objective of the shared vision.

The realisation of the shared vision and the scientific knowledge outcome were influenced by the elements of the interactive learning process: the *prime mover, network formation, intermediary* and *knowledge flows*. During the emergence of the DNC, stakeholders with nutrition and genetics expertise joined forces. The scientific knowledge outcome was dependent on the combination of the complementary knowledge of these stakeholders. *Prime mover* Unilever identified possibilities in nutrigenomics and contacted complementary stakeholders. During the research activities the *knowledge flows* between the stakeholders and a combination of these flows of knowledge eventually resulted in scientific insights as e.g. codified in scientific articles. *Intermediary* functions, in the form of exemplification projects organised by TNO and mouse models, were in place for the understanding and the combination of complementary scientific knowledge. The *knowledge flows* accumulated into scientific insights. These scientific insights made it evident that nutrigenomics research was very complex, far more complex than anticipated at the beginning of the DNC. As a consequence, the DNC stakeholders placed more emphasis on the unravelling of the factors involved with metabolic stress. Consequently, the stakeholders were only able to realise the first objective of the shared vision; the understanding of metabolic stress increased, but not to the level that novel food components (i.e. the second objective) could be developed.

In turn, the interactive learning process was influenced by the conditions for interactive learning (i.e. the proximities). The prime mover and network formation of the DNC were influenced by geographical, cognitive, regulatory and social proximity. While the network was being formed, the regulatory proximity at the meso level was constructed, i.e. the mutual agreement that dealt with IPR and NDA issues. The *knowledge flows* in the interactive learning process of the DNC were influenced by the geographical, cognitive, regulatory, social and organisational proximity. There was a *cognitive distance* – based on different technological foci – between the stakeholders participating in the DNC. At the same time, the stakeholders were confident that they would be able to learn from each other. Within the DNC different *'intermediaries'* were discernible: sometimes the intermediary can be attributed to a single stakeholder (e.g. TNO in the exemplification projects), but intermediating objects were also discernible (i.e. mouse models) that helped to bridge the cognitive gap between the stakeholders. The numerous amounts of formal and informal face-to-face interactions within the DNC facilitated knowledge flows and interactive learning between the stakeholders. The knowledge flows between the stakeholders were facilitated through the presence of trust (social proximity) and IPR arrangements (regulatory proximity at the meso level). Through the *mutual agreement,* which encompassed IPR -arrangements and 'non-simultaneously', unwanted spill-overs were prevented. The mutual agreement had a positive effect on the knowledge interchange and interactive learning within the DNC because it enabled the stakeholders to share knowledge freely without worrying about spill-overs. The *organisation* of the DNC in work packages created *flexibility* for the individual stakeholders to perform their research, while at the same time their efforts were *coordinated* through the DNC (i.e. the integrating work package WP I).

Regarding cultural proximity, we observed a difference in management culture between the CMSB and WCFS. It was said that CMSB managers interacted with researchers on a daily basis, whereas contact between WCFS managers and the researchers was more formalised in progress meetings. This interpretation of culture differs from our operationalisation of cultural proximity, which was based on the difference in underlying incentive structure for research institutes and companies. Due to the informal character of the management culture in the CMSB there might have been a more open and free culture which could have had a positive influence on knowledge creation. At the same time it could also be argued that daily contact between managers and researchers had a restrictive effect on the flexibility to perform research because researchers might feel that they were constantly monitored. If that was the case, then the more 'distant' form of management pursued by the WCFS might have left more room for the individual researchers to perform their research in a more flexible manner. Since management style was not incorporated into cultural proximity we use this observation to make recommendations for further research in Chapter 7.

# 6 Interactive Learning in the German Competence network Metabolic Syndrome

In this chapter we explore the FILET in the case of the German Competence network Metabolic Syndrome (CMS). We start with a short introduction of the emergence of the CMS consortium and its surrounding context (§6.1). In the three following sections we answer the *sub-questions* of the analytical framework (see §4.7):

6. *What was the interactive learning outcome of the consortium?*
7. *How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process?*
8. *How were the elements of the interactive learning process influenced by the conditions for interactive learning?*

The sub-questions provide insight into the interactive learning outcome of the CMS (§6.2), the interactive learning process, and how that process influenced the outcome (§6.3), and the conditions for interactive learning and how these conditions influenced the interactive learning process (§6.4). We conclude and discuss the case study findings in §6.5[57].

## 6.1 Origination and context of the CMS

The CMS was a nutrigenomics consortium in Berlin/Brandenburg in the period 2003-2006. The consortium consisted of the Charité-Universitätsmedizin Berlin[58], the Deutsches Institut für Ernährungsforschung (Dife), the Max-Planck Institute für Molekulare Genetik, and Unilever Bestfoods ((Netzwerk Nutrigenomforschung Berlin/Brandenbrug 200x) – see also Figure 34). The stakeholder at the Charité-Universitätsmedizin Berlin was specialised in hypertension research and had access to patient material, the Max-Planck Institute normally worked on cardio-vascular diseases, focusing specifically on the heart, and was specialised in Single Nucleotide Polymorphisms (SNPs) analysis methods and statistics. Dife performed obesity research for which they used polygenic mouse models. The research foci on hypertension, heart disease and obesity are related through the Metabolic Syndrome. This expertise of the various stakeholders on different research methods could contribute to the research performed within the CMS: the goal of the CMS was to identify gen-polymorphisms

57 We reflect on the FILET in the final chapter of this book.

58 During the existence of the CMS this stakeholder moved from the Charité-Universitätsmedizin Berlin to the University Hospital of Münster (UKM)/Leibniz-Institut für Arteriosklerosеforschung (LIFA).

connected with hypertension and the development of patient therapies on the basis of the research insights[59]. The consortium received funding through BioProfile for the period 08/2003-07/2006 (Netzwerk Nutrigenomforschung Berlin/Brandenbrug) to an amount in the region of € 3 million (interview 2007-10-01).

Since the mid-1990s there have been three successive nationwide biotechnology stimulation programmes in Germany: BioRegio, BioProfile and BioChancePlus. BioProfile was set up in November 1999 as part of the Biotechnology Stimulation Plan 2000 in Germany (Bundesministerium für Bildung und Forschung 2005). *"BioProfile is a development programme of the German federal ministry for science and technology (BMBF) to expand the industrial application of academic knowledge in the life sciences"* (www.nutrigenomik.de 1-9-2008). BioProfile was particularly oriented towards regions that focus on *"future-oriented fields of application of modern biotechnology"* (www.bmbf.de/en/962.php 1-9-2008)[60]. Regions that wished to become eligible for funding had to submit a proposal. Of the 30 interested regions, 20 submitted a proposal, three of which were funded. One of these regions was Berlin/Brandenburg. Situated within Berlin/Brandenburg were the Charité-Universitätsmedizin Berlin (one of the largest hospitals in Europe with approximately 1 million patients a year), three technical universities, research institutes and companies. In general it can be said that the focus of the regional innovation system of Berlin/Brandenburg was on biotechnology, nutrition and molecular diagnostic systems (interviews 2007-10-04, 2007-10-05). Based on the historical focus in the region on biotechnology and nutrition and the focus of BioProfile three professors in Berlin/Brandenburg joined forces and wrote a proposal that concentrated on food-related diseases for the Berlin/Brandenburg region. They formed the Verein zur Förderung der Nutrigenomforschung[61] (interview 2007-10-05). This proposal was awarded a budget of € 18 million for the period 2003-2010 to fund application-related projects in the field of nutrigenomics (www.nutrigenomik.de 1-9-2008). This budget had to be matched by the SMEs that would participate in projects of the Verein zur Förderung der Nutrigenomforschung. Formally, the SMEs had to match 40-50% of the BioProfile funding (interview 2007-10-05). The SMEs in Berlin/Brandenburg were typically 5-10 years old, employed 10 FTE and were unable to completely match the BioProfile grant (interview 2007-10-04). Therefore, in practice the matching totalled 20-40%, which was approximately € 8.5 million (interview 2007-10-05). The organisations that participated in projects funded by the Verein zur Förderung der Nutrigenomforschung also invested indirectly by allowing their equipment to be used, providing technical support, etc.

The Verein zur Förderung der Nutrigenomforschung financed so-called 'innovation projects' with the BioProfile funds for Berlin/Brandenburg. These projects ranged from basic research to novel product development and the formation of spin-offs. Proposals for innovative projects were evaluated by the scientific advisory committee

59 As we described in §3.3 hypertension is one of the diseases that is part of the Metabolic Syndrome. This is a major problem that can be addressed through nutrigenomics.

60 For more information on the BMBF [the German federal ministry for science and technology] and BioProfile visit www.bmbf.de/en/962.php

61 In English: Society for the Stimulation of Nutrigenomics research

of the Verein zur Förderung der Nutrigenomforschung as well as an external reviewer (interview 2007-10-04; 2007-10-05). Several selection criteria were in place (interview 2007-10-04):

- The proposal had to be application-oriented[62]; and therefore,
- Industry had to be involved and preferably have a coordinating task within the innovation project;
- A large risk should be involved, which would make it unlikely for a single organisation to invest in the research;
- The topic had to be nutrigenomics related;
- The project quality had to be very high;
- Projects should span 2-3 years (interview 2007-10-05).

Although the name Verein zur Förderung der Nutrigenomforschung suggests a clear focus on nutrigenomics, in practice the innovation projects were more diverse: e.g. 'PorkChip', 'Minimal invasive blood sugar sensor', and 'Genetics and pharmacogenomics of obesities' (www.nutrigenomik.de 1-9-2008). Two reasons were accountable for this broad interpretation of nutrigenomics. First, the focus of the organisations within Berlin/Brandenburg was broader than nutrigenomics alone. Organisations were interested in a wide range of subjects in the fields of biotechnology, nutrition and molecular diagnostic systems (interviews 2007-10-04, 2007-10-05). Therefore, organisations applied for funding under the heading of nutrigenomics-related research, while in practice their research was not by definition related to nutrigenomics specifically. Second, the political and social climate in Germany was somewhat reserved towards GMO-related research and research that might be associated with GMOs (interview 2007-10-05). GMO-related research was actually banned under the Red/Green government and therefore organisations reformulated their research into non-GMO-related research, such as nutrigenomics[63]. One recent example of the negative sentiment in Germany towards GMO-related research was the premature termination of insect and/or fungal resistant GM maize field trials in 2008. Universities decided to discontinue or not to start these field trials under public pressure from politicians, the general public, media, activists and their supporters (Schiermeier 2008).

Due to the wide focus of the Verein zur Förderung der Nutrigenomforschung, only one of the 23 funded innovation projects was a nutrigenomics consortium (interview 2007-10-05): *"therapy innovation for the Metabolic Syndrome with a focus on hypertension"*. This consortium is also referred to as the Competence network Metabolic Syndrome (CMS). The focus of the CMS consortium on hypertension originated from the project initiator, who was specialised in hypertension research

62 *"The BMBF [the German federal ministry for science and technology] (almost) only funds applied research (and not basic research) and therefore companies have to be involved in the interdisciplinary multi-stakeholder projects."* (interview 2007-10-05)

63 GMOs are Genetic Modified Organisms. Nutrigenomics is research into the relationship between the genome, nutrition and disease risks. This research is not automatically related to GMO, but new ingredients – identified through nutrigenomics research – for functional foods could be produced with the help of GMO.

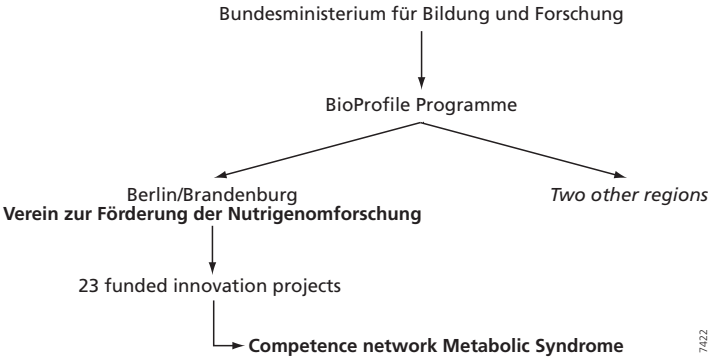


**Figure 31** Overview of the funding construction of CMS and relation between organisations

(interview 2007-10-02). The first proposal for the CMS was rejected by the scientific advisory committee of the Verein zur Förderung der Nutrigenomforschung because it was not multidisciplinary enough and did not have a specific focus. The Verein zur Förderung der Nutrigenomforschung advised the CMS *"to incorporate other institutes*[64] *as well in order to have a more interdisciplinary approach"* (interview 2007-10-02) and to focus on a specific disease. This became hypertension since that was the main topic of interest of the project initiator.

In this section we described the origination of the Verein zur Förderung der Nutrigenomforschung that funded the Competence network Metabolic Syndrome (CMS). It explained the policy context in which the CMS consortium was embedded (Figure 31). In the next sections we focus on interactive learning within the CMS consortium.

## 6.2 Interactive learning outcome of the CMS

In this section we answer the first sub-question of the analytical framework:
6. *What was the interactive learning outcome of the consortium?*

First we describe the interactive scientific knowledge outcome (6.2.1). Hereafter, we give a description of the realisation of the shared vision which encompasses the shared vision that was co-constructed at the beginning of the CMS in 2003 and the extent to which the stakeholders had realised this shared vision at the end of the CMS in 2006 (§6.2.2). The findings are summarised in §6.3.3. These descriptions of the interactive scientific knowledge outcome and the realisation of the shared vision are the starting points for §6.3 in which we analyse *how* the interactive learning outcome was influenced by the interactive learning process.

64 Dife was already involved in preparing the first proposal. Ultimately, Dife did not take part in this first proposal because it was not related closely enough to Dife's expertise. In the second proposal, Dife – now with different researchers – became one of the stakeholders within the CMS (interview 2007-10-02).

### 6.2.1 Interactive scientific knowledge outcome

The interactive scientific knowledge outcome consists of (co-)publications, (co)patents, applications, standardisation (codified), and an increase in know-how, expertise and problem solving capacbilities (tacit) (See Table 8 in §4.7).

At the end of the research period the CMS had to produce a final report for the Verein zur Förderung der Nutrigenomforschung (Brand and Brand-Herrmann 2006). This final report also contained an overview of the codified scientific knowledge outcome of the CMS. In all, the CMS produced 28 scientific articles[65] (Annex V). Since these articles provide detailed insight into the specific scientific knowledge that resulted from the research within the CMS we take a closer look at them[66]. The articles were published in a wide range of journals like the Journal of Hypertension, Obesity and Metabolism, Pharmacogenomics, Kidney International and Stroke. This diversity of journals indicates the wide range of nutrigenomics research and the diseases that are categorised under the Metabolic Syndrome. Noteworthy in this respect is that while the term 'Metabolic Syndrome' occurs in some of the scientific articles, the term 'nutrigenomics' is not mentioned at all. However, as explained in Chapter 3, nutrigenomics and the Metabolic Syndrome are closely intertwined. Nutrigenomics is a blanket concept that covers a wide range of knowledge fields and methods. One of the articles is a study design (Staessen, Kuznetsova et al. 2005), but the majority of them present scientific findings. In general terms the scientific articles of the CMS describe the relation between candidate gene (variants) and hypertension (e.g. (Funke-Kaiser, Reichenberger et al. 2003; Rodriguez and Palou 2004; Zhang, Staessen et al. 2006) and (Brand, Wang et al. 2003) (see Figure 32) cardio-vascular disease (e.g. (Kuznetsova, Staessen et al. 2004; Kuznetsova, Staessen et al. 2004)), cholesterol (e.g. (Brand-Herrmann, Kuznetsova et al. 2005)) and obesity (Freson, Stolarz et al. 2006 in revision). Sometimes there is a focus on specific sections of the population (e.g. Chinese (Li, Staessen et al. 2006) or on White Europeans (Olszanecka, Kawecka-Jaszcz et al. 2002)). The scientific articles of the CMS also indicate the difficulties surrounding nutrigenomics research. Often, multiple genes and gene-gene interactions are involved in pathways that may lead up to a disease and contribute to the Metabolic Syndrome. It proved very difficult to state conclusive findings as e.g. exemplified by these statements:

*"Intensive research over the past two decades has so far failed to identify common genetic polymorphisms with a major impact on blood pressure or associated cardiovascular phenotypes, suggesting that multiple genes each with a minor impact, along with gene-gene and gene-environment interactions, play a role."* (Kuznetsova, Staessen et al. 2006)

*"Since the result for the -532C/-20A/-18C/-6G haplotype was due to differences between non-carriers and carriers of this haplotype on both chromosomes, a recessive inheritance model for BP effects could be assumed."* (Brand-Herrmann, Köpke et al. 2004)

65 The final report of the CMS reported 23 articles (Brand and Brand-Herrmann 2006), additionally five articles were reported by interviewee 2007-10-02 5.

66 At the time of this analysis some articles had not yet been published. We were only provided with published articles for the analysis.

The 28 scientific articles written by the stakeholders within the CMS contain no co-publications: *"We don't have publications where different network people joined on a publication"* (interview 2007-10-01). Co-publications are generally regarded as a clear indicator for interactive learning outcome. However, this does not automatically imply that the scientific articles are not the result of interactive learning because not all collaborations are automatically granted with a co-authorship. For instance one interviewee stated that the collaboration in the CMS *"is a win-win situation because no one can publish without the other persons"* and therefore *"there have been publications which were clearly produced from this knowledge out of the consortium"* (interview

# An epidemiological study of blood pressure and metabolic phenotypes in relation to the G$\beta_3$ *C825T* polymorphism

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***Background*** **The *825T* allele of the G-protein $\beta_3$-subunit gene is associated with increased intracellular signalling and adipogenesis in experimental studies. We studied the *C825T* polymorphism in relation to blood pressure, obesity and intermediate phenotypes in a Caucasian population.**

***Methods*** **We genotyped 737 men and 775 women (participation rate, 64.3%) enrolled in a Belgian population study. Dichotomous phenotypes were tested for association with the *C825T* polymorphism by Fisher's exact test and multiple logistic regression. For continuous traits, we used analysis of covariance and generalized estimating equations.**

***Results*** **The *T* allele (39.7 versus 29.1%) and *TT* genotype (16.1 versus 7.7%) were more prevalent in obese men than in non-obese men ($P \leq 0.01$). *TT* homozygous men, compared with *C allele* carriers, had higher daytime ambulatory blood pressure (mean systolic/diastolic differences, 3.6/2.5 mmHg; $P \leq 0.02$), higher body weight (2.7 kg, $P = 0.04$), greater risk of obesity (risk ratio, 1.90; $P = 0.005$), increased triceps skinfold thickness (2.3 mm, $P = 0.007$), higher serum insulin concentration (4.1 mU/l, $P = 0.006$), more insulin resistance ($P = 0.01$), and increased erythrocyte count ($0.11 \times 10^{12}$ cells/l, $P = 0.04$) and haematocrit (0.9%, $P = 0.02$). In women, haematocrit and erythrocyte count were also higher ($P \leq 0.03$) in *T* allele carriers, but other phenotypes were not correlated with the *C825T* polymorphism.**

***Conclusion*** **Male and female carriers of the *T* allele at position 825 of the G-protein $\beta_3$-subunit gene have a slightly higher haematocrit and erythrocyte count. Male *TT* homozygotes have a higher blood pressure and are more obese and insulin-resistant than *C allele* carriers. We speculate that the higher blood pressure in *TT* homozygous men might arise via a metabolic pathway characterized by obesity and insulin resistance as well as via increased peripheral resistance secondary to the higher haematocrit. *J Hypertens* 21:729–737 © 2003 Lippincott Williams & Wilkins.**

**Journal of Hypertension** 2003, 21:729–737

**Keywords: blood pressure, gender, genes, G-protein, haematocrit, insulin resistance, obesity**

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Sponsorship: The FLEMENGHO Study was supported by research grants G.0174.97 and G.0291.98 from the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (Brussels, Belgium) and a special research grant from the Katholieke Universiteit Leuven (Onderzoekstoelage OT99/28). Nuclear families were recruited in the framework of the European Project on Genes in Hypertension, which is supported by the European Union (contract numbers IC15-CT98-0329-EPOGH and QLG1-CT-2000-01137-EURNETGEN). The genetic laboratory was financed in part by a research grant from the Universitätsklinikum Benjamin Franklin, Berlin, Germany (FSP-EB 1999/2000). J.-G.W. was supported by the bilateral scientific collaboration between the People's Republic of China and Flanders, Belgium (BIL 02/10). S.-M.H. received grants from the Deutsche Forschungsgemeinschaft (Graduierten-Kolleg 426/2-00, Molekularbiologische Grundlagen der Therapie and Graduierten-Kolleg 754, Myokardiale Genexpression und Funktion, Myokardhypertrophie).

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**Received** 19 August 2002 **Revised** 28 November 2002
**Accepted** 13 January 2003

**See editorial commentary page 683**

## Introduction

Guanine nucleotide regulatory proteins (G-proteins) are part of the intracellular signalling cascades [1]. Their activation is the principal mechanism through which stimulated heptahelical receptors generate changes in intracellular function [1]. Siffert and coworkers identified a common *C825T* polymorphism in exon 10 of the $\beta_3$-subunit of the heterotrimeric G-protein [2]. The *825T* mutant is associated with a splice variant, which shortens the protein by 41 amino acids and produces a gain of function [2]. Increased signalling by G-proteins stimulates adipogenesis [3] and may lead to obesity [4]. In addition, *C825T* is a candidate polymorphism for hypertension, because the mutation entails stimulation of the ubiquitously expressed $Na^+/H^+$ exchanger [5]. At the kidney level, this may increase $Na^+$ re-absorption and cause chronic volume expansion [6]. Prevention of intracellular acidosis may also lead to proliferation of vascular smooth muscle cells, vascular remodelling and increased peripheral arterial resistance [6]. However, published reports on the association between hypertension and the *825T* mutation produced inconsistent results [2,7–9].

**Figure 32** Example of one of the CMS scientific articles (Brand, Wang et al. 2003)

2007-10-01). The precise influence of the interactive learning process on the scientific articles outcome is difficult to assess because it is impossible to determine which elements are the result of tacit knowledge that was gained through interaction with a particular stakeholder.

Scientific articles are one form of codified scientific knowledge outcome. Other codified outcomes are patents, applications (e.g. functional foods or nutrigenetics tests) and standardisation. The CMS research did not lead to a patent or an application and we observed no activities within the CMS that resulted in standards that could be used to facilitate the exchange of data and knowledge between the stakeholders.

Besides the codified interactive scientific knowledge outcome of the CMS, represented by the scientific articles, there is also the tacit interactive scientific knowledge outcome within the CMS in the form of an increase in know-how, expertise and problem solving capabilities. The Max-Planck Institute was specialised in SNPs analysis methods and was able to increase their expertise on this technology through their research within the CMS. This increase in expertise made it possible to use the same techniques at a lower cost (interview 2007-10-01). The SNPs analysis methods developed by the Max-Planck Institute were transferred to the University Hospital of Münster, where they were used to screen patient materials for specific genes. However, at the beginning the researchers at the University Hospital of Münster had some difficulties with these new methods: *"[A] post-doc of my lab [i.e. the Max-Planck Institute] – who developed the technology – joined the [University Hospital of Münster] crew for a period of time and trained them. Also a PhD Student of the Münster-lab joined us for a week to learn further advanced methods"* (interview 2007-10-01). In this way, University Hospital of Münster researchers increased their know-how and expertise on SNPs analysis methods, which were developed and improved by the Max-Planck Institute. As such, the ability to use new technology is a result of the interactive learning process between the Max-Planck Institute and the University Hospital of Münster. The Max-Planck Institute and Dife discussed technical and analytical issues, through which Dife *"learned how to generate cheap high throughput micro-arrays"* (interview 2007-10-02). Dife and the Max-Planck Institute continued their collaboration after the CMS came to a close because they were highly satisfied with their collaboration and knowledge exchange within the CMS. Additionally, the Max-Planck Institute continued to perform SNPs analysis methods for Dife. This was a cost-effective solution for Dife because it was a cheaper solution than if Dife had to perform their own analysis (interview 2007-10-02). Dife and the Max-Planck Institute met during collaboration in the CMS, and their continued collaboration is an outcome of the interactive learning process within the CMS.

The CMS project coordinator also mentioned additional outcomes that were – according to her – contributable to the research within the CMS (interview 2007-10-17).

- The coordinator herself was appointed to a DFG Heisenberg professorship;
- The scientific knowledge gained from the CMS research was used to write new research proposals which have been accepted by funding agencies (Brand and Brand-Herrmann 2006);

- An additional learning effect of the CMS might be the diffusion of knowledge among the participants (e.g. industry) that attended the Verein zur Förderung der Nutrigenomforschung 's annual status seminar, at which all innovation project leaders presented their findings (interview 2007-10-04).

For these additional outcomes it is difficult to specifically attribute the developments to collaboration within the CMS; other factors might also have played a role in the appointment to the Heisenberg professorship and the funding of new research. This also applies with regard to the diffusion of knowledge through the annual status seminar.

### 6.2.2 Realisation of the shared vision

The concept of *realisation of shared vision* captures the co-construction of a shared vision by the stakeholders at the beginning of the consortium and the extent to which the stakeholders were able to realise this shared vision at the end of the consortium. The shared vision encompasses a i) perceived problem, ii) a common goal, iii) the formulated objectives, and iv) the approach taken on how to reach these objectives and goal (codified in e.g. mission statements). In this section we present the shared vision that was co-constructed at the beginning of the CMS and the extent to which this shared vision was realised by the stakeholders at the end of the CMS.

The high prevalence of hypertension in Germany was conceived as a major problem. While the CMS was being formed Germany had the highest incidence of hypertension with 55.3% (Wolf-Maier, Cooper et al. 2003) (Table 11). This considerable welfare and health care problem for Germany could be addressed with nutrigenomics research within the CMS (interview 2007-10-17).

The common goal for the CMS was to find a solution for hypertension: *"Identifying functionally relevant candidate gen-polymorphisms for high blood pressure and determination of individual genetic risk profiles as a basis for innovative nutrigenomics and pharmacogenomics therapy in high blood pressure patients."* (Netzwerk

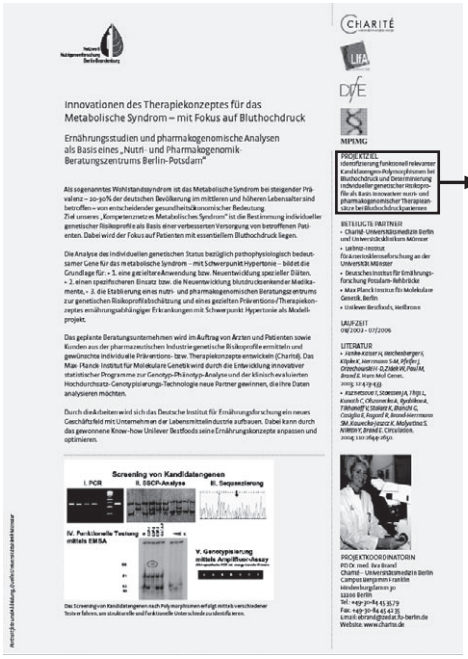
**Table 11** Hypertension incidence overview of the Wolf-Maier study (Wolf-Maier, Cooper et al. 2003), showing the highest prevalence in Germany with 55.3%

| Counrty | Prevalence % | | | Hypertensive Presons Taking Medication % | BMI |
|---|---|---|---|---|---|
| | All | Men | Women | | |
| *North America* | 27.6 | 30.4 | 24.8 | 44.4 | 27.1 |
| United States | 27.8 | 29.8 | 25.8 | 52.5 | 27.4 |
| Canada | 27.4 | 31.0 | 23.8 | 36.3 | 26.8 |
| *Europe* | 44.2 | 49.7 | 38.6 | 26.8 | 26.9 |
| Italy | 37.7 | 44.8 | 30.6 | 32.0 | 26.4 |
| Sweden | 38.4 | 44.8 | 32.0 | 26.2 | 26.5 |
| Engeland | 41.7 | 46.9 | 36.5 | 24.8 | 27.1 |
| Spain | 46.8 | 49.0 | 44.6 | 26.8 | 27.4 |
| Finland | 48.7 | 55.7 | 41.6 | 25.0 | 27.1 |
| Germany | 55.3 | 60.2 | 50.3 | 26.0 | 27.3 |

Nutrigenomforschung Berlin/Brandenbrug 200x) (Figure 33). The common goal encompassed two complementary objectives: 1) to increase the understanding of gen-polymorphisms in relation to hypertension and 2) to apply this gained insight in patient therapy. The approach to reach the objectives of the CMS project was organised along research strands: each stakeholder had his own research strand and milestones that had to be met (interviews 2007-10-01, 2007-10-17; email conversation with interviewee 2007-10-02):

1. The Max-Planck Institute would develop/improve SNPs analysis methods and transfer them to the University Hospital of Münster;
2. The Max-Planck Institute would perform analyses for Dife;
3. Dife would perform polygenic mouse studies, the findings from which would be transferred to the University Hospital of Münster;
4. The University Hospital of Münster would construct a patient database;
5. The University Hospital of Münster would use the SNPs analyses method from The Max-Planck Institute to screen patients for the candidate genes identified by Dife;
6. Another Max-Planck institute department would perform statistical analyses for the University Hospital of Münster.

According to the interviewees, the shared vision acted as a driver for the innovative research performed by the stakeholders within the CMS project (e.g. interviews 2007-10-01, 2007-10-02, 2007-10-17). As such, the shared vision created awareness about the problem and the goal to be reached by the CMS.


Innovationen des Therapiekonzeptes für das Metabolische Syndrom – mit Fokus auf Bluthochdruck

Ernährungsstudien und pharmakogenomische Analysen als Basis eines „Nutri- und Pharmakogenomik-Beratungszentrums Berlin-Potsdam"

Screening von Kandidatengenen

I. PCR II. DSCP-Analyse III. Sequenzierung

IV. Funktionelle Testung mittels EMSA

V. Genotypisierung mittels Amplifluor-Assay

PROJEKTKOORDINATORIN



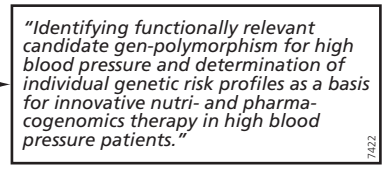



**Figure 33** Common goal ("Projektziel" in German) of the CMS as codified in an informative leaflet (Netzwerk Nutrigenomforschung Berlin/Brandenbrug 200x)

Now that we have described the elements of the shared vision the CMS started out with, the question is now to what extent this shared vision was realised by the stakeholders at the end of the CMS. During the existence of the CMS the perceived problem and common goal would remain the same, but at the end of the CMS (2006) the stakeholders had only realised the first of the two objectives. This was partly due to the complexity of the scientific research and the resulting findings (as we will see in §6.3). Also, not all the milestones set by the CMS were reached.

### 6.2.3 Summarising the interactive learning outcome

The interactive learning outcome is summarised in Table 12. The interactive scientific knowledge outcome of the CMS was codified in 28 scientific articles. The Max-Planck Institute increased it's tacit know-how and expertise regarding SNPs analysis methods. This method was transferred to the University Hospital of Münster where the know-how, expertise and problem solving capabilities regarding this method were increased. Dife learned how to perform microarrays from the Max-Planck Institute. These two stakeholders continued their collaboration, even after the end of the CMS.

At the beginning of the CMS (2003), the shared vision of the CMS consisted of the perceived problem of hypertension in Germany and the goal became to find a solution for this problem. Therefore, the objectives were to gain further insight into gen-polymorphisms and hypertension and to start genetic counselling on the basis of their research. In order to achieve the objectives of the CMS the research was organised along three research strands and milestones. At the end of the CMS, the stakeholders had only realised the first objective.

**Table 12** the interactive learning outcome of the CMS

| | |
|---|---|
| Interactive scientific knowledge outcome | • 28 publications, no co-publications but partly dependent on interactive learning<br>• no standardisation<br>• increase in know-how<br>• increase in expertise<br>• problem solving capabilities<br>• continued collaboration between Dife and the Max-Planck Institute<br><br>*Additional*<br>• new projects funded by organisations other than the Verein zur Förderung der Nutrigenomforschung<br>• DFG Heisenberg professorship<br>• dissemination to participants through annual seminar |
| Realisation of the shared vision | • perceived problem: prevalence of hypertension in Germany<br>• common goal: to find additional treatment for hypertension through nutrigenomics<br>• objectives: 1) to increase the understanding of gen-polymorphisms in relation to hypertension and *2) to apply this gained insight for patient therapy [not realised]*<br>• approach: research strands |

## 6.3 Interactive learning process in the CMS

In this section we answer the second sub-question of the analytical framework:

7. *How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process?*

For the analysis we describe the influence of all elements of the interactive learning process (i.e. prime mover, network formation, intermediary and knowledge flows) on the interactive scientific knowledge outcome (§6.3.1) and the influence on the co-construction and realisation of the shared vision (§6.3.2). The findings of the influence of the interactive learning process on the interactive learning outcome are summarised in §6.3.3.

### 6.3.1 Interactive learning process and interactive scientific knowledge outcome

During the formation of the CMS the first initiative to form the consortium and to collaborate was taken by a Charité-Universitätsmedizin Berlin professor (interview 2007-10-01, 2007-10-02, 2007-10-17). This *prime mover* identified the possibility to obtain funding from the Verein zur Förderung der Nutrigenomforschung for her research on hypertension, which motivated her to write a project proposal. The funding requirements of the Verein zur Förderung der Nutrigenomforschung stipulated that the research must be specifically related to nutrigenomics. The prime mover realised that it was not possible to *"acquire this new knowledge alone"*, while at the same time a *"collaboration could result in more output"* (interview 2007-10-17). Driven by this sense of urgency for collaboration, the prime mover contacted stakeholders from fields that were able to contribute complementary knowledge, expertise and resources (e.g. research facilities) for nutrigenomics research on hypertension. Therefore, the prime mover started the *formation of a network* that would become the CMS. One group of the Max-Planck Institute was contacted for their work on SNPs analysis methods and another for their statistical analyses (interview 2007-10-17). Dife became involved in the CMS because of its expertise with polygenic mouse models (interview 2007-10-02). The expectation was that the combination of these knowledge fields and expertises would result in a scientific outcome that could contribute to realising the shared vision of the CMS, that was: 1) to increase the understanding of gen-polymorphisms in relation to hypertension and 2) to apply this gained insight for patient therapy. Since the application of scientific results was one of the funding requirements of the Verein zur Förderung der Nutrigenomforschung, companies were often involved in collaborations like the CMS. Unilever Bestfoods, a manufacturer of (functional) foods, became a formal stakeholder because of the potential application of the research results for nutrition concepts. This CMS network of stakeholders was granted funding by the Verein zur Förderung der Nutrigenomforschung. As soon as the funding was received, the actual research was started in August 2003.

During the research performed within the CMS, the difference in expertise between the CMS stakeholders resulted in *knowledge flows* between them (Figure 34). The Max-Planck Institute developed and improved the SNPs analysis methods that could be used for the screening of patient material on candidate genes for hypertension

(Rickert, Borodina et al. 2004)[67]. As soon as the Max-Planck Institute's SNPs analysis methods were set up, they were transferred to the University Hospital of Münster where the screening could be performed. This technology transfer was arranged through the exchange of researchers. The Max-Planck Institute would also perform SNPs analysis methods for Dife (i.e. milestone 2, see §6.2.2). During the existence of the CMS the analyses for Dife were only performed with test samples and not with material resulting from the research performed within the CMS. Nevertheless, during the CMS research there was a great deal of discussion and interaction about technical and methodological issues between the Max-Planck Institute and Dife (email conversation with interviewee 2007-10-02)

Dife used a mouse that not only developed obesity but also insulin resistance and hypertension. Through the crossing of this so-called New Zealand obese mouse with lean strains – like the SJL or C57BL/6 mouse – association studies could be performed. These studies resulted in 15 QTLs (Quantitative Trait Loci) related to hypertension. At the same time, the effect of different diets on the same genotype of mice that resulted in different phenotypes could be studied. This research resulted in 3-4 candidate genes related to hypertension that were transferred to the University Hospital of Münster. Dife received no feedback from the University Hospital of Münster regarding the research on the candidate genes identified by Dife (personnel communication with interviewee). The results of the polygenic mouse studies could be used by the University Hospital of Münster to screen patient cohorts with the SNPs analyses method provided by the Max-Planck Institute. One of the candidate genes[68] identified by Dife was still under study at the University Hospital of Münster when the CMS ended in July 2006 (interview 2007-10-02). Another research group at the Max-Planck Institute would perform statistical analyses for the University Hospital of Münster (i.e. milestone 6, see §6.2.2). At the end of the existence of the CMS consortium the Max-Planck Institute had received the first data sets for statistical analyses, but these analyses had not yet been performed (Brand and Brand-Herrmann 2006). Ultimately the *knowledge flows* between the stakeholders and the increase in stakeholders' knowledge was codified in the scientific articles, as described in §6.2.1.

Although Unilever Bestfoods was a formal stakeholder within the CMS, they were not directly involved in the research performed within the consortium. In practice, activities within the CMS can be described as basic, fundamental research. The possible future application of this research could give Unilever an early advantage: *"most of the time it is basic research which generates knowledge that on the long run could be used by companies to make a product out of it or commercialise it"* (interview 2007-10-05).

The research of and interactions between the CMS stakeholders is visualised in Figure 34.

67 NB This article is not part of the scientific knowledge outcome of the CMS, but was part of a different project (GABI 2004).

68 Removal of this gene in mice resulted in hypertension being independent of body weight.

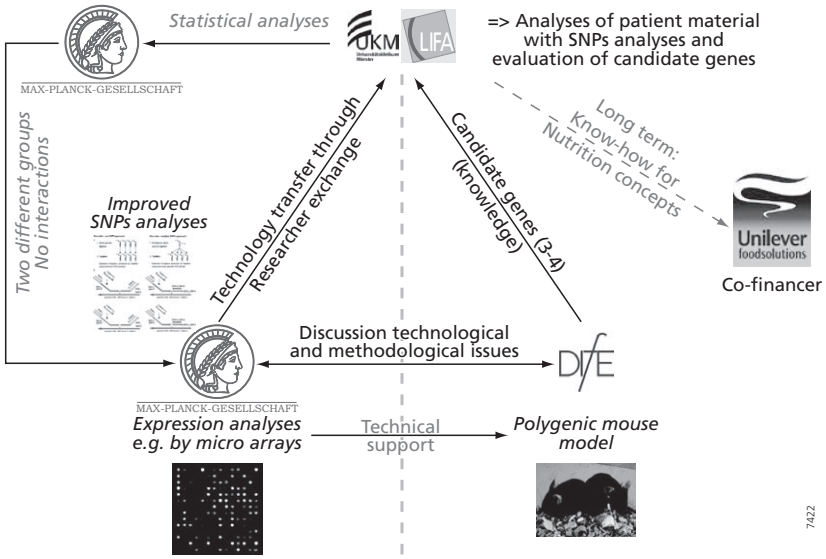



**Figure 34** CMS stakeholders, their research, and knowledge flows between them. In light grey the interactions/milestones that were planned, but not (completely) carried out (based on interviews and email conversations)

The stakeholders within the CMS had different expertises and used different techniques for their research. Therefore these stakeholders were not familiar with all the techniques employed by the other stakeholders in the consortium. During their presentations at meetings each stakeholder put extra emphasis on explaining the methods they used to the other stakeholders. As such, the stakeholders themselves acted within the network as *intermediaries* translating scientific knowledge and know-how (interview 2007-10-17).

To summarise: the initiative of the *prime mover* and the *network formation* set the scene for the research within the CMS that was characterised by the research activities of the individual stakeholders and the *knowledge flows* between them. The interactions between the stakeholders and the resulting knowledge flows are responsible for the scientific insights that led to the *interactive scientific knowledge outcome*. This interactive scientific knowledge outcome is codified in scientific articles that were partly dependent on the interactive learning process. On the tacit dimension, the interactive learning process in the CMS resulted in an increase of know-how, expertise and problem solving capabilities through technology transfer between the stakeholders.

### 6.3.2 Interactive learning process and the realisation of the shared vision

The CMS started with a shared vision comprising a perceived problem, a common goal, objectives and an approach to reach these objectives. The perceived problem was the incidence of hypertension in Germany, and the common goal was to find a solution for this problem. To reach this goal, two common objectives were

formulated: 1) to gain insight into hypertension gen-polymorphisms, and 2) to set up a hypertension clinic. In order to achieve this common goal and meet the objectives a research approach was organised along three research strands and milestones that each stakeholder had to meet.

The shared vision of the CMS was co-constructed at the beginning of the CMS. This co-construction was an 'attuning process' between the vision of the Verein zur Förderung der Nutrigenomforschung and the CMS (Figure 35). A vision for the CMS had to be in line with the funding demands. The overall goal of the BioProfile programme was "*to expand the industrial application of academic knowledge in the life sciences*" (www.nutrigenomik.de 1-9-2008). Within this national programme the focus of the Verein zur Förderung der Nutrigenomforschung within the Berlin/Brandenburg region was the stimulation of food-related biotechnology research, which had to be application-oriented as well. Since the expertise of the CMS *prime mover* was on hypertension, this subject became the starting point for the perceived problem. Nevertheless, in order to obtain funding from the Verein zur Förderung der Nutrigenomforschung the CMS had to present a common goal that contained both food-related biotechnology research and applications. This dual conformity explains the two objectives: *"Identifying functionally relevant candidate gen-polymorphisms for high blood pressure and determination of individual genetic risk profiles as a basis for innovative nutri- and pharmacogenomics therapy in high blood pressure patients."* (Netzwerk Nutrigenomforschung Berlin/Brandenbrug 200x) (Figure 33). In order to gain insight into hypertension gen-polymorphisms and to develop patient therapies, the prime mover was dependent on complementary knowledge from other stakeholders since the prime mover was not familiar with 'nutrigenomics research' and research techniques. Therefore, the prime mover contacted stakeholders on the basis of their specific expertise, such as SNPs analysis methods for the screening of patient data.

During the network formation the prime mover's vision was adopted by the other stakeholders and became the shared vision of the stakeholders (e.g. interviews 2007-10-01, 2007-10-02, 2007-10-17). However, the stakeholders still had their individual visions. The individual vision of the Max-Planck Institute was to refine its SNPs analysis methods, and for Dife it was to refine their mouse studies. The difference in individual visions was due to the fact that the only stakeholder with direct expertise on hypertension was the Charité-Universitätsmedizin Berlin, whereas the other stakeholders had different complementary expertises that they normally employed for research on other topics than hypertension. The individual visions were not contrary to the shared vision and contributed to the fulfilment of the shared vision. E.g. the mouse studies performed by Dife contributed to Dife's individual vision of developing their mouse study techniques, while at the same time the mouse studies contributed to the overall consortium shared vision of gaining insight into gen-polymorphisms and hypertension. As such, the individual visions were not in conflict with the overall consortium shared vision because they all fell under the umbrella of the shared vision. The individual visions are also reflected in the research approach taken by the CMS: There were three relatively separate research strands in which each stakeholder could pursue his own vision. Eventually, all knowledge and information from the research

strands was transferred to the prime mover where the knowledge was combined in order to gain insight into hypertension and develop patient therapies on the basis of these insights, i.e. the two objectives of the shared vision (see also Figure 34).

During the existence of the CMS the prevalence of hypertension in Germany remained high. As such, the perceived problem did not alter, nor did the common goal of the CMS. The individual research strands (Figure 34) were carried out by the stakeholders, but not all the milestones (i.e. milestone 6 in §6.2.2) that were envisioned in order to reach the objectives of the shared vision were realised by the end of the CMS in 2006. During the actual research carried out within the CMS the *knowledge flows* between the stakeholders (see Figure 34) accumulated into the interactive scientific knowledge outcome, which encompassed insight into the gen-polymorphisms connected with hypertension. Through these insights it also became evident to the stakeholder that the second of the two objectives of the shared vision (i.e. to develop patient therapies) was too ambitious or unrealistic and could therefore not be realised. This is not only contributable to the efforts within the CMS consortium, but also an effect of the general advances in genomics and hypertension research at that moment. During the existence of the CMS (08/2003-07-2006), only about 10-15% of the genes that influence hypertension were known (interview 2007-10-02). Thus, the majority of the genes concerned and their role in hypertension were unknown. *"This aim [i.e. development of patient therapies] has not been fulfilled and is still in progress. The one PhD student could not fulfil all the goals the network had. So a lot of information from other people outside the network was inserted into this project, but nevertheless not all genes that are responsible for the MS were identified."* (interview 2007-10-02). Thus, the second objective of the CMS could not be fulfilled due to the scientific research findings resulting from the knowledge flows in the interactive learning process[69]. The individual stakeholders were able to fulfil their individual vision, namely increasing their know-how and expertise regarding the research techniques they employed.

To summarise: the prime mover started the formation of a vision that would be a guideline for the funding application and research within the CMS. During the network formation, the prime mover's vision became a shared vision among the stakeholders because under the umbrella of the shared vision the stakeholders could pursue their individual visions, which were related to their research expertises. During the research performed within the CMS consortium the knowledge flows between the stakeholders resulted in scientific insights on the basis of which the stakeholders could realise half of the objectives: The stakeholders gained insight into the gen-



69 The second objective of the CMS was the application of the research findings for patient therapy. For this purpose a genetic counselling hypertension clinic would be developed. At the end of the CMS a "hypertension ambulance" was set up at the University Hospital of Münster: *"persons with (a high risk for) hypertension are treated by dieticians, sport instructors and stress managers in order the 'prevent' hypertension and the use of medicines"* (interview 2007-10-07). This hypertension ambulance does not provide genetic counselling as envisioned, but is based on 'classical' insights about hypertension. The genetic profile is not used because *"up to now only 10-15% of the genes that play a role are known. Therefore it would not make sense to screen the patients for these few genes"* (interview 2007-10-07).

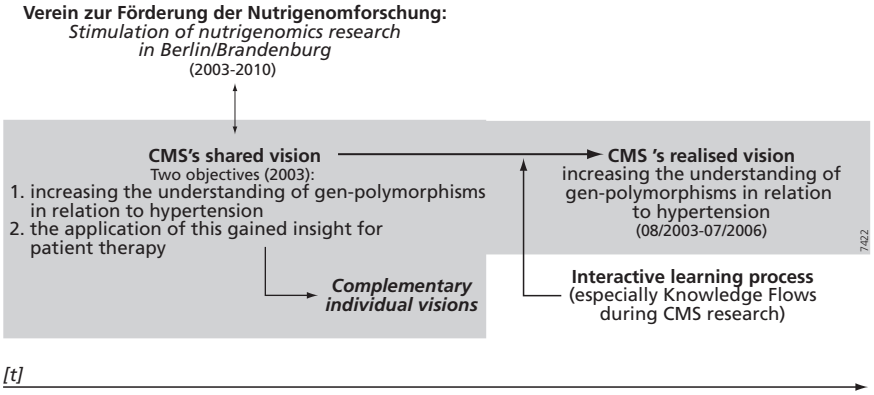



**Figure 35** Co-construction and realisation of the co-constructed shared vision of the CMS

polymorphisms involved in hypertension (first objective). However, the scientific research findings also showed that the development of patient therapies, as the second objective, was too ambitious for the time being.

### 6.3.3 Summarising the interactive learning process and interactive learning outcome

During the formation of the CMS the prime mover had the main role in constructing the vision. During the actual formation of the network the prime mover's vision became the shared vision of the stakeholders involved because the prime mover's vision provided and umbrella under which the stakeholder could pursue their individual vision which were related tot their research expertises. The main activity of the prime mover during the formation was to identify possibilities for research and funding and to mobilise the most appropriate stakeholders during network formation. The knowledge flows of the interactive learning process during the research eventually led to the scientific knowledge outcome. However, it is very difficult to assess the actual degree to which the scientific articles are the result of interactive learning. The tacit components of the scientific knowledge outcome show a more direct dependency on the interactive learning process: the Max-Planck Institute widened its experience on SNPs analysis methods, and the University Hospital of Münster became able to work with these new technologies. The Max-Planck Institute and Dife even continued their collaboration after the end of the CMS. This would not have happened without the knowledge flows between the stakeholders in the consortium. Based on the scientific knowledge outcome that resulted from the knowledge flows in the interactive learning process, the stakeholders could not realise the second objective of the shared vision, i.e. the development of patient therapies for hypertension.

## 6.4 Conditions for interactive learning in the CMS

In the previous section we explained how the interactive learning process (i.e. the prime mover, network formation, intermediary and knowledge flows) influenced the interactive learning outcome of the CMS consortium (i.e. the interactive scientific

knowledge outcome, and realisation of the shared vision). In this section we answer the third sub-question of the analytical framework:

8. *How were the elements of the interactive learning process influenced by the conditions for interactive learning?*

For each condition of interactive learning (i.e. geographical, cognitive, regulatory, cultural, social and organisational proximity) we analyse how the conditions influenced the interactive learning process (§6.4.7 – §6.4.7). For this analysis we look at the prime mover, network formation and knowledge flows. The intermediary is not part of this analysis because no stakeholder was identified within the CMS consortium that acted as an intermediary. The findings of the influence of the conditions for interactive learning on the interactive learning process are summarised in §6.4.7.

### 6.4.1 Geographical proximity

The CMS was funded through the BioProfile programme, which was particularly oriented towards the stimulation of regions. Therefore, one of the funding requirements was that most of the consortium's stakeholders must be located within the Berlin/Brandenburg region. The CMS consisted of the Charité-Universitätsmedizin Berlin, Deutsches Institut für Ernährungsforschung (Dife), Max-Planck Institute für Molekulare Genetik and Unilever Bestfoods. This *agglomeration* of stakeholders was located in the Berlin/Brandenburg region. Unilever Bestfoods in Heilbronn was also a stakeholder in the CMS but had no part in the actual research. During the existence of the CMS the prime mover, who was working at the Charité-Universitätsmedizin Berlin, was given a new affiliation and moved to the University Hospital of Münster(UKM)/ Leibniz-Institut für Arterioskleroseforschung (LIFA). This is approximately 400 km to the west of Berlin/Brandenbrug and therefore the geographical distance between the prime mover and the CMS consortium increased (interview 2007-10-04).

The original agglomeration of the stakeholders within the Berlin/Brandenburg region allowed the *prime mover* to arrange face-to-face meetings with complementary stakeholders. The agglomeration in Berlin/Brandenburg not only facilitated the prime mover in her search for suitable stakeholders, but also allowed the stakeholders concerned to meet face-to-face. As such, the geographical proximity facilitated the *network formation*. During the first meetings in the network formation the stakeholders assessed whether they could collaborate and learn from each other: *"to see if we got the feeling we can work together"* (interview 2007-10-01). The face-to-face meetings during formation of the network enabled the exchange of complex and tacit knowledge. For example, the stakeholders discussed their expertises and how they could contribute to the research within the CMS. At the same time, the stakeholders adapted a shared vision that encompassed their individual visions. The stakeholders also assessed whether they could trust each other during the collaboration.

The geographical proximity between the CMS stakeholders also facilitated face-to-face meetings during the actual research: the stakeholders met every six months in a seminar room at the Max-Planck Institute (because of its central location in Berlin) in order to update each other on the progress that had been made, to exchange information, and to discuss how the partners could help one another (interview 2007-

10-02, 2007-10-05). These meetings *"also made it possible to identify successful and less successful research and to make decisions about which topic to focus on"* (interview 2007-10-17). Each year there was a mandatory 2-hour meeting for the Verein zur Förderung der Nutrigenomforschung (from which a representative was present) in Berlin, during which the stakeholders gave a short presentation on their progress. An annual status seminar was also held during which all the research funded by the Verein zur Förderung der Nutrigenomforschung was represented. One-to-one informal contacts were also arranged in the periods between these formal meetings. For example, Dife and the Max-Planck Institute discussed technical and methodological issues (email conversation with interviewee 2007-10-02). Researchers were also exchanged for the purpose of exchanging knowledge between the stakeholders. A post-doc and a PhD of the Max-Planck Institute stayed at the University Hospital of Münster, and a PhD of the University Hospital of Münster visited the Max-Planck Institute. These visits created *temporary geographical proximity,* which allowed for the interchange of tacit knowledge and expertise on new technologies that were (to be) employed during the research. Thus, knowledge flows between the stakeholders were facilitated by the geographical proximity, which allowed for face-to-face meetings in which tacit and complex knowledge was interchanged. However, there was only a limited number of formal meetings and most knowledge flows seem to have come about during one-to-one interactions between stakeholders and the exchange of researchers.

To summarise: the agglomeration of the stakeholders in Berlin/Brandenburg facilitated the prime mover and the network formation during formation of the CMS: at the early meetings the stakeholders assessed whether they could trust each other and whether they thought they could learn from one another. During the actual research within the CMS, the knowledge flows were influenced through the face-to-face meetings between stakeholders that were facilitated through the agglomeration and temporary geographical proximity. Temporary geographical proximity was for instance achieved through the exchange of researchers between the stakeholders.

### 6.4.2 Cognitive proximity

The stakeholders participating in the CMS had different *technological foci*. The expertise of Charité-Universitätsmedizin was on hypertension and patient studies, Dife's expertise was on obesity research and mouse studies, and the Max-Planck Institute's expertise was on the cardio-vascular system, SNP analysis methods and statistical analyses. The technological focus and overlap can also be assessed through the journals the stakeholders published in, and co-citation and cross-citation analysis of the scientific articles resulting from the CMS. Articles from Dife and the Charité-Universitätsmedizin Berlin were published in different journals[70]. The co-citation analyses in Figure 36 show a clear grouping of articles and (co-)citations from the Charité-Universitätsmedizin Berlin (on the right of the dotted line) and Dife (on the left). Of the total number of 649 references, Dife and the Charité-Universitätsmedizin Berlin only share three. There are no cross-citations between the Dife and Charité-Universitätsmedizin Berlin articles. These findings further indicate the cognitive distance between the stakeholders' technological foci.

70 The Max-Planck Institute reported/provided no articles/work in progress.

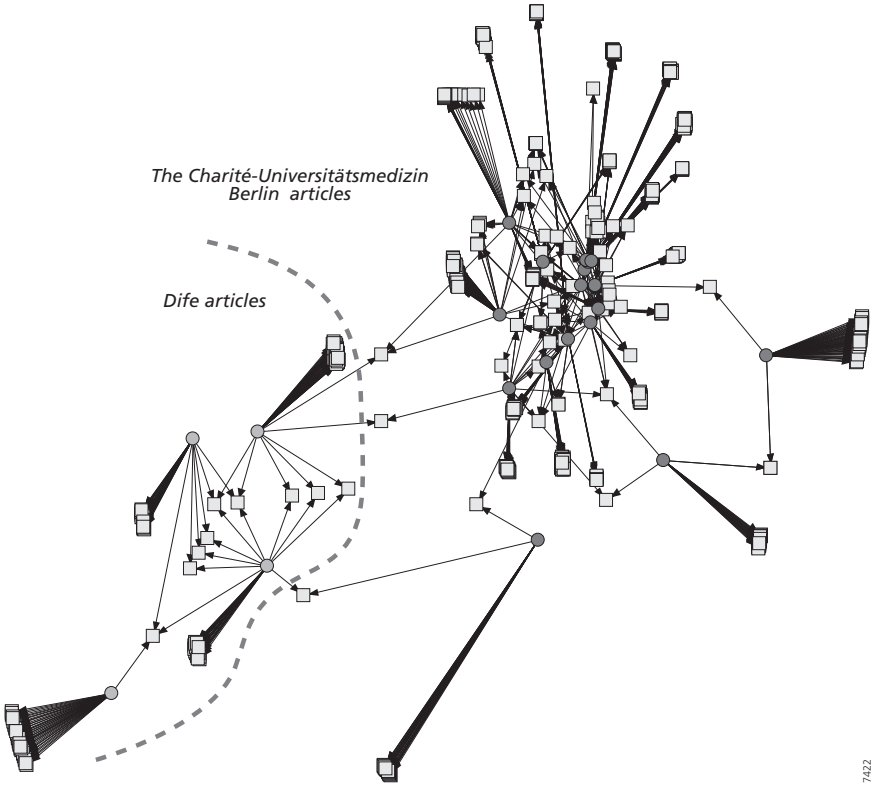



**Figure 36** Co-citation analyses of CMS articles with Usenet6 based on CMS scientific articles (●=article, ■= citations). Dife articles on the left hand side. One outlier (with no co-citations with other articles) was removed from the graphical presentation))

Thus, the CMS consisted of stakeholders with different technological foci both in research expertise and their fields of knowledge: the Charité-Universitätsmedizin Berlin was specialised in hypertension research and had access to patient material, the Max-Planck Institute normally worked on cardio-vascular diseases and the associated research focused on the heart and employed SNPs analysis methods, and Dife performed obesity research and used polygenic mouse models. Obesity, cardio-vascular disease and hypertension are related through the Metabolic Syndrome. A combination of these expertises could generate insights into gen-polymorphisms affiliated with hypertension. Based on the interactive scientific knowledge outcome of the CMS consortium, it seems that the stakeholders were able to bridge the cognitive distance between them. The stakeholders produced scientific articles and showed an increase in know-how, expertise and problem solving capabilities, which was (at least partly) dependent on the collaboration within the CMS.

The *prime mover* identified new research challenges for hypertension within the emerging field of nutrigenomics. In order to gain new insights into hypertension through nutrigenomics research, complex complementary knowledge had to be

combined. The consequence of this was that stakeholders with different technological foci needed to be involved, and that a cognitive distance existed between them. Since the expertise of the prime mover was on hypertension, she started to contact complementary stakeholders with different expertises. The necessity to combine complementary knowledge was also recognised by the other stakeholders. Therefore, the cognitive distance had a positive effect on *the network formation*. During the network formation the stakeholders had to assess whether they could cross the knowledge difference between them during the network formation.

The CMS stakeholders had to collaborate in order to achieve advancements in the field of hypertension with the help of nutrigenomics research. The cognitive distance between the CMS stakeholders was of influence on the *knowledge flows* between the stakeholders because knowledge from different stakeholders had to be combined. For example, Dife used its expertise with mouse models to identify candidate genes for hypertension. But in order to scan patient cohorts for these candidate genes, expertise from the Max-Planck Institute on SNPs analysis methods, and the experience of University Hospital of Münster with patient material had to be brought in as well. While there was a cognitive distance between the stakeholders regarding their research focus and experience with research methods, they were still able to understand each other's work. For example, the Max-Planck Institute employed the SNPs analysis methods for the identification of diagnostics markers (interview 2007-10-01) and as such the Max-Planck Institute *"was simply applying techniques that were developed for heart disease in this network [i.e. CMS] for blood pressure"* (interview 2007-10-01). The stakeholders reported on their findings at the meetings. Since these findings were based on the stakeholders' specific knowledge and methods used, the stakeholders also explained the methods they employed (e.g. the Max-Planck Institute SNPs analysis method) to the other stakeholders. This allowed them to bridge the potential knowledge gaps between them.

To summarise: a cognitive distance was a prerequisite for interactive learning in the CMS where complementary knowledge on hypertension, SNPs analysis and mouse models had to be combined. This requirement influenced the prime mover to mobilise stakeholders that were able to contribute this complementary knowledge. During the network formation the stakeholders assessed whether they could bridge the cognitive distance between them and whether they could indeed collaborate. During the actual research, the difference in technological foci stimulated the flow of knowledge between the stakeholders because different expertises had to be combined in order to gain new insight into hypertension through nutrigenomics research.

### 6.4.3 Regulatory proximity

Regulatory proximity is divided into regulatory proximity at the *macro* and at the *meso* level.

*Regulatory proximity at the macro level* refers to i) regulations and ii) the availability of government funding. Since all the CMS stakeholders were located in Germany they were subject to the same regulations. Germany is a Member State of the EU and nowadays most legislation is directly related to the EU directives. During the

existence of the CMS (08/2003-07/2006) one regulation was important with regard to nutrigenomics and functional foods:

- Proposal for a regulation of the European Parliament and of the council on nutrition and health claims made on foods (COM (2003) 424)[71]. According to the proposal only scientifically substantiated food and health claims will be allowed after evaluation by the European Food Safety Authority (EFSA).

Since the CMS focused on basic research on hypertension in order to arrive at new patient therapies, it was not influenced by legislation related to functional foods. The stakeholders had to comply with other regulations at the macro level regarding the scientific research that would be performed within the CMS. For example, the Charité-Universitätsmedizin had to comply with regulations regarding the use of patient material, and Dife had to comply with regulations regarding mouse studies; the mouse studies had to be approved and the animal facilities were visited by government officials (interview 2007-10-02). At the macro level, government funding is another factor that could have an influence on the interactive learning process. The Verein zur Förderung der Nutrigenomforschung made funding available for nutrigenomics research (see §6.1).

The *prime mover* was acquainted with basic research and the associated regulations, and therefore aware of which regulations the research had to comply with. Since scientific research always had to comply with regulations governing scientific research (e.g. related to handling patient material and performing animal tests), these regulations gave no extra certainty or uncertainty and therefore neither stimulated nor hindered the particular actions of the prime mover (e.g. starting the formation of a network in order to perform research). Since the research within the CMS could be funded through the Verein zur Förderung der Nutrigenomforschung there was no uncertainty in terms of actual research financing. This 'certainty' stimulated the prime mover to finalise her ideas and start the formation of the CMS. The availability of funding stimulated the stakeholders to *form a network*. Funding of the CMS research was very important and only when the grant had been awarded could the collaboration start: *"If you don't get the money, the collaboration would not work because you cannot do anything without a grant"* (interview 2007-10-01).

*Regulatory proximity at the meso level* refers to issues between stakeholders on agreements that deal with Intellectual Property Rights (IPR) and Non-Disclosure Agreements (NDA). Collaboration between the stakeholders within the CMS was drawn up in a mutual agreement between the stakeholders. Since the CMS was one of the innovation projects funded by the Verein zur Förderung der Nutrigenomforschung, the stakeholders also had to sign a contract ('Zuwendungsbescheid') with the BMBF[72].

71 NB This proposal was made in 2003 and was accepted by the EU council on 12 October 2006. Since then it is known as EU Regulation 1924/2006 (see http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:EN:PDF). At the time of the existence of the CMS, the proposal still had to be ratified by all EU Member States.

72 The BMBF is the German federal ministry for science and technology that provided the funds to the Verein zur Förderung der Nutrigenomforschung.

These contracts dealt with IPR and NDA issues. In general, the agreements stipulated that no knowledge would leave the consortium before all stakeholders concerned agreed (interview 2007-10-02): if a stakeholder wanted to publish or apply for a patent, then that stakeholder would have to involve the other stakeholders that contributed to the research findings. The CMS coordinator (i.e. the prime mover) had to be involved in all patent and publication processes (interview 2007-10-02). For the Max-Planck Institute, the content of this arrangement was checked by their legal department (interview 2007-10-01). Dife had a contract with a law firm that checked the legal issues for Dife regarding contracts, patents, etc. (interview 2007-10-02).

*Knowledge flows* between the stakeholders were stimulated through the mutual agreement between the stakeholders and the contract signed with the BMBF (the so-called 'Zuwendungsbescheid'). The agreements reduced the risk of potential, unwelcome knowledge spill-overs outside the CMS, and thereby stimulated the flow of knowledge between the stakeholders within the CMS. One example of this free flow of knowledge between the CMS stakeholders is when Dife discovered a new candidate gene and immediately informed all the other stakeholders (interview 2007-10-02). Dife was confident that this discovery would not 'spill over' the boundaries of the consortium.

To summarise: EU legislation with regard to functional foods did not apply to the CMS because the CMS research was not directed towards the development of functional foods. Since the CMS would only perform basic research, the stakeholders had to comply with the research regulations they had always been required to comply with when handling patient material and using animal models. These research regulations did not create any uncertainty about the research that could be performed. The prime mover and network formation were influenced by the funding programme because the funding allowed the stakeholders to perform the research without having to worry about financing. The flows of knowledge between the stakeholders were influenced by the contracts that limited unwelcome spill-overs. This facilitated the free flow of knowledge between the stakeholders.

### 6.4.4 Cultural proximity

The CMS consisted of research institutes (i.e. Dife and the Max-Planck Institute), university hospitals (i.e. Charité-Universitätsmedizin Berlin/University Hospital of Münster) and one company (i.e. Unilever Bestfoods). Unilever had become involved because cooperation with a company was needed in order to fulfil the funding requirements. At the same time, linking up with the research within the CMS was an opportunity for Unilever to keep itself informed about new developments in nutrition-related research, of which the resulting knowledge might eventually be used for the development of new functional foods. Since Unilever did not actively participate in the actual research, the organisations within the CMS can be characterised as public research institutes. In general, the underlying incentive for research institutes are publications. Within the CMS the stakeholders were not only focused on publications but also on patents: "*In Germany this [dual focus] is independent of the institution*" (interview 2007-10-01). Based on this dual focus on publications and patents, the

participating stakeholders operated under the same underlying incentive structure, namely the focus on both patents and publications.

Since there was no cultural distance between the stakeholders regarding the incentive structure, the *prime mover* did not have to be aware of any conflicting interests of the stakeholders she was contacting. For the stakeholders that were mobilised by the prime mover it also became evident that they operated under the same incentive structure, which stimulated them to collaborate (*network formation*).

During the actual research, the stakeholders were aware of the fact that advancements could only occur through collaboration, which could result in scientific findings that could be codified in scientific articles (the dominant outcome of scientific work). This scientific culture facilitated the *flow of knowledge* between the stakeholders. The stakeholders were aware that they were dependent on each other's research and therefore had to share the scientific knowledge resulting from their individual research strands in order to create publications and patents.

To summarise: the stakeholders had the same outcome focus and therefore the prime mover was not influenced by potential conflicts of interest between the stakeholders in the consortium. The similar underlying incentive structure for the stakeholders stimulated the network formation of the CMS. The shared culture of the stakeholders had a facilitating effect on the knowledge flows between the stakeholders during the actual research because knowledge sharing could lead to publications and patents.

### 6.4.5 Social proximity

Prior to the formation of the CMS, only the *prime mover* (i.e. Charité-Universitätsmedizin Berlin) was acquainted with the other stakeholders from previous collaborations, and therefore only the prime mover had a shared history with the other stakeholders (interview 2007-10-01). Based on this shared history, the prime mover knew she could trust these stakeholders within the CMS. During the actual research, trust amongst the stakeholders would facilitate the free flow of knowledge between the stakeholders. Therefore, the presence of trust was important for the prime mover when she started to mobilise stakeholders that could contribute complementary knowledge.

As described above, apart from the prime mover, the stakeholders were unfamiliar with one another. The stakeholders had to assess whether they could trust each other during the collaboration. The first meetings of the stakeholders during the *network formation* were therefore used to build up trust between the stakeholders: *"you have to meet each other in order to find if you get the feeling you can trust each other"* (interview 2007-10-01). The outcome of these first meetings was that the stakeholders were convinced they could trust each other and this was a stimulus to start the collaboration. Whether the stakeholders really trusted each other would only become evident during the actual research. The interchange of staff (interviews 2007-10-02, 2007-10-17) between the stakeholders, and therefore the free access to each other's research facilities and

knowledge databases[73], indicated the presence of actual trust among the stakeholders: *"The network operated as a community, sharing the required information"* (interview 2007-10-17). According to one interviewee, working closely together on a topic was a *"really good basis for trusting each other"* (interview 2007-10-01). The presence of trust had a positive influence on the *knowledge flows* between the stakeholders. Information was shared freely within the CMS *"otherwise it wouldn't make sense to have a network"* (interview 2007-10-01). When, for example, candidate genes were identified, this new knowledge was freely distributed in the CMS (interview 2007-10-02; 2007-10-17): *"you have to trust your partners that they do not transfer the knowledge to someone else [..] otherwise everyone will work for his own"* (interview 2007-10-02).

To summarise: the shared history of the prime mover with the other stakeholders, the exchange of staff and the open access of research facilities and research data among the stakeholders indicates the presence of trust between them. This presence of trust had a positive influence on the knowledge flows within the CMS.

### 6.4.6 Organisational proximity

The CMS was a virtual network of complementary stakeholders. The involved stakeholders dedicated their knowledge, manpower and research facilities to the CMS. For example, one post-doc from the Max-Planck Institute worked full time for the CMS. Furthermore, the research group leader of the Max-Planck Institute contributed intellectually to the CMS project (interview 2007-10-01).

The structure of the CMS was arranged during the network formation and it had an influence on the knowledge flows during the actual research. Each stakeholder knew which research to perform within his research strand and to whom the resulting knowledge would have to be transferred. The structure of the CMS 'dictated' the knowledge flows between the stakeholders. The research was divided among the stakeholders and each stakeholder was flexible in performing his own research in order to achieve his own milestones. For example, the University Hospital of Münster's tasks were to develop a databank with 600 individuals, constructing different new cohorts, identifying genes and their functions, gene-gene interactions and environment-gene interactions (i.e. milestones 4 and 5 in §5.2.2) (interview 2007-10-17). All the research was coordinated by the project coordinator (i.e. the prime mover). Through this set up the individual stakeholders were free to perform their own research within the CMS. The knowledge that resulted from the stakeholders' individual research strands was transferred to the prime mover. However, there were limited feedback loops from the prime mover to the individual mile stones (personal communication with interviewee). Thus, all knowledge was combined, but the combined knowledge from the stakeholders was not fed back to the individual stakeholders (see also Figure 34). As such, the organisation was typified by flexibility of the individual stakeholders and limited coordination of the prime mover.

73 It was not always necessary for stakeholders to use e.g. the databases of other stakeholders: Dife generated data which were analysed by the Max-Planck Institute. In other words, Dife generated primary data and therefore it was not necessary for Dife to use any other database.

To summarise: the organisational proximity was arranged during formation of the CMS. The research within the CMS was organised in three research strands and milestones. Through the research strands, each stakeholder knew which tasks to perform and to whom the resulting knowledge had to be transferred. The organisation into research strands was therefore a blueprint for the knowledge flows within the CMS. The organisation proved to be flexible but lacked in coordination (i.e. lacking feedback of accumulated knowledge).

### 6.4.7 Summarising the interactive learning conditions and interactive learning process

The CMS was an agglomeration of stakeholders in the Berlin/Brandenburg region (i.e. high *geographical proximity*). The stakeholders all came from different complementary knowledge fields and therefore there was some *cognitive distance* between them. The CMS had to comply with the normal regulations for research (*regulatory proximity at the macro level*) and was therefore not affected by regulations related to functional foods. At the macro level, funding for nutrigenomics research was available through the Verein zur Förderung der Nutrigenomforschung. The *regulatory proximity at the meso level* between the stakeholders was determined by the mutual agreement drawn up between them. The CMS stakeholders involved in the research activities within the CMS were research institutes with the same dual outcome focus, i.e. on publications and patents (i.e. *cultural proximity*). The stakeholders trusted each other (i.e. *social proximity*): The prime mover already had a shared history with the other stakeholders. The stakeholders with no shared history built up trust during the network formation. Throughout the research within the CMS the stakeholders exchanged researchers and had free access to each other's databases. How the CMS was organised allowed the individual stakeholders to shape their own research (i.e. flexibility), nevertheless, feedback and coordination within the CSM were lacking (i.e. coordination). When the milestones were reached, knowledge was transferred to the project coordinator. Feedback from the coordinator to other stakeholders was for the most part lacking.

The availability of government funding opened up opportunities for the financing of nutrigenomics research on hypertension, which stimulated the prime mover and the other stakeholders to form a network. The geographical distance between the stakeholders made it easy for the prime mover to meet up with them. The cognitive distance between the prime mover and the other stakeholders was a prerequisite for the combination of complementary knowledge fields needed to study hypertension through nutrigenomics. The cognitive distance between the stakeholders resulted in knowledge flows between the stakeholders. The combination of complementary knowledge could lead to new insights regarding hypertension.

The stakeholders trusted each other, which was a stimulus for forming the CMS. The presence of trust between the stakeholders became perceptible during the actual research in the form of knowledge and researcher exchanges between stakeholders. During the actual research, temporary geographical proximity between the stakeholders facilitated face-to-face meetings in which complex and tacit knowledge could be interchanged. The presence of trust and the mutual agreement prevent any unwelcome spill-over.

## 6.5 Conclusion and discussion

In this chapter we explored the FILET in the German Competence network Metabolic Syndrome (CMS). We applied the analytical framework in order to find an answer to the second part of the leading research question for our research:

*How can interactive learning in emerging technologies be conceptualised, and* ***how can this conceptualisation provide insights into interactive learning between heterogeneous stakeholders in nutrigenomics?***

The *interactive learning outcome* of the CMS consisted of the interactive scientific knowledge outcome and the realisation of the co-constructed shared vision. The *prime mover* created a vision that was based on the prevalence of hypertension in Germany. Due to this prevalence, the goal of the CMS was to find a solution to the hypertension problem. Two objectives were formulated: to gain insight into hypertension gen-polymorphisms and to develop patient therapies.

The prime mover's vision was adopted as a shared by the other stakeholders during *network formation* because this vision acted as an umbrella under which the stakeholders could fulfil their individual visions. The individual stakeholders wished to increase their specific know-how and expertise on hypertension, SNPs analysis and mouse models respectively. Since their know-how and expertise was required for the nutrigenomics research, the individual visions contributed to the shared vision. Therefore, the shared vision that was co-constructed at the beginning of the CMS is an umbrella for the individual visions that contributed to that shared vision.

The *knowledge flows* within the CMS led to the stakeholders' combined complementary knowledge, which accumulated in the interactive scientific knowledge outcome: insight into gen-polymorphisms for hypertension. Through the scientific insights the stakeholders could- for the time being – only realise the first of the two objectives of the shared vision. The *interactive scientific knowledge outcome* comprised 28 scientific articles and an increase in the stakeholders' know-how, expertise and problem solving capabilities. Within the CMS there was no stakeholder that apparently acted as an *intermediary*.

The dimensions of proximity influenced the interactive learning process: nutrigenomics research on hypertension required the combined complementary knowledge from heterogeneous stakeholders. Therefore, the cognitive distance between the stakeholders was a prerequisite for interactive learning. The regulatory proximity at the macro level opened up funding opportunities for this research. Based on these starting points the prime mover contacted complementary stakeholders in Berlin/Brandenburg with whom she was already familiar (social proximity). The geographical agglomeration facilitated the *prime mover* in these contacts and during the *network formation* the geographical proximity allowed for face-to-face meetings in which learning opportunities and trust were assessed by the stakeholders concerned. Regulatory proximity at the meso level (i.e. mutual agreement on e.g. IPR) was created during the network formation. There was no cultural difference between the stakeholders that were contacted since they all had a dual focus on publications and patents. As such, cultural proximity seemed to have no influence on the prime

mover or network formation. Cognitive distance between the stakeholders resulted in *knowledge flows*. And knowledge flows of tacit and complex knowledge were facilitated by the (temporary) geographical, social and regulatory proximity at the meso level. The combination of complementary knowledge was further accomplished through the organisational proximity; each stakeholder knew which research had to be performed and with whom the resulting findings had to be interchanged.

The research carried out within the CMS did not result in any co-publications between the stakeholders collaborating in the CMS. This finding might be explained by an observation in the case study. For instance, we found that stakeholders were flexible within their own research strand and that all resulting knowledge was transferred to the project coordinator. However, the stakeholders that were interviewed reported a lack of feedback from the project coordinator and consequently the individual stakeholders might have been dependent on their own research and experiments alone to produce scientific articles instead of co-publishing results with other stakeholders in the consortium. Although the scientific knowledge outcome did not contain any CMS co-publications, it is interesting to see that most articles were written in collaboration with researchers from other organisations. The research that resulted in these articles was not only funded through the Verein zur Förderung der Nutrigenomforschung, but also through a variety of government funds. For example, a substantial number of the articles[74] were also funded through The European Project on Genes in Hypertension (EPOGH)[75]. This finding might indicate the stakeholders' dependency on multiple funding in order to perform the necessary research. This might also explain the dual outcome focus of the CMS stakeholders (i.e. both on publications and patents). This dual outcome for research institutes is typical of the German research system in which research institutes are supposed to acquire research funds from different sources (Heinze and Kuhlmann 2008). Patenting research findings might then act as an extra source of income if the patent is sold or licenced to a commercial party.



74 (Olszanecka, Kawecka-Jaszcz et al. 2002; Kuznetsova, Staessen et al. 2004; Kuznetsova, Staessen et al. 2004; Kuznetsova, Staessen et al. 2004; Stolarz, Staessen et al. 2004; Wojciechowska, Staessen et al. 2004; Brand-Herrmann, Kuznetsova et al. 2005; Kuznetsova, Staessen et al. 2006; Freson, Stolarz et al. 2006 in revision)

75 *"A large-scale, family-based study in which participants from seven different populations were phenotyped and genotyped according to standardized procedures."* (Kuznetsova, Staessen et al. 2006)

# 7 Conclusion, discussion and recommendations

Interactive learning has been a central concept in innovation studies since the 1980s and its influence on innovation has been shown in numerous studies since then. Interactive learning is of special importance in emerging technologies in which complementary and tacit knowledge has to be exchanged and combined in order to learn and innovate. However, sufficient insight into the black box of the interactive learning process has been lacking thus far. Therefore, the purpose of our research was to improve the insight into interactive learning of heterogeneous stakeholders in the context of emerging technologies such as nutrigenomics. In line with this we formulated the following *central research question*:

*How can interactive learning in emerging technologies be conceptualised, and how can this conceptualisation provide insights into interactive learning between heterogeneous stakeholders in nutrigenomics?*

In order to answer this question we divided our research into two parts. In Part I we developed the Framework for Interactive Learning in Emerging Technologies (FILET) and in Part II we explored the FILET in two nutrigenomics consortia. We start this concluding chapter by summarising the answers to the sub-questions answered in Part I (§7.1) and the 'intermezzo' in which we discussed nutrigenomics (§7.2). In §7.3 we draw conclusions regarding the case studies in Part II at a more aggregate level. We then discuss the research design, the empirical findings of the case studies, and the internal and external validity of the FILET (§7.4). In §7.5 we make recommendations for further research, stakeholders and policy makers. We end this book with a closing statement (§7.6).

## 7.1 The FILET

In Part I we answered three sub-questions which helped us develop the Framework for Interactive Learning in Emerging Technologies:

1. *What is the outcome of the interactive learning process in emerging technologies?*
2. *What are the elements of the interactive learning process and how do they influence the interactive learning outcome?*
3. *What are the conditions for interactive learning and how do they influence the interactive learning process?*

The developed FILET is a heuristic that can help us to understand interactive learning in emerging technologies (Figure 37). Interactive learning is a process with an outcome and the process itself is influenced by conditions. The outcome of interactive learning

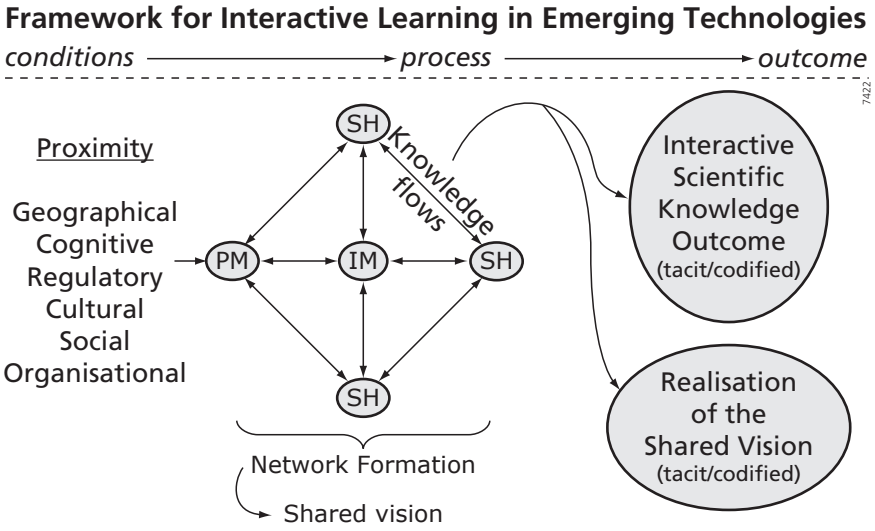



**Figure 37** The developed Framework for Interactive Learning in Emerging Technologies (PM=Prime Mover; IM=InterMediary; SH=StakeHolder)

can be divided into an *interactive scientific knowledge outcome* and the *realisation of the shared vision*, which comprises the co-construction of a shared vision by the stakeholders at the beginning of the collaboration and the extent to which the stakeholders are able to realise that shared vision. The interactive learning outcome is influenced by the main elements of the interactive learning process. These elements include the *prime mover, network formation, intermediary,* and the *knowledge flows* between the stakeholders: the prime mover takes the initiative to bring complementary stakeholders together[76]. During the network formation the complementary stakeholders start to form a consortium. The knowledge flows contain the knowledge that is produced and exchanged between the stakeholders. An intermediary can help in translating knowledge and bridging any potential knowledge gaps between the individual stakeholders. The interactive learning process is influenced by conditions that facilitate the exchange of tacit knowledge. These conditions are the *geographical, cognitive, regulatory, cultural, social,* and the *organisational proximity*. Geographical proximity refers to the physical distance between stakeholders and cognitive proximity to the distance between their technological foci. Regulatory proximity refers to (inter) national regulations, government funding and mutual agreements that can influence the interactive learning process. Cultural proximity refers to the informal rules adhered to by the stakeholders. Social proximity refers to the presence of trust between stakeholders and organisational proximity indicates the flexibility and coordination of research within the consortium.

In this section we presented a summary of the building blocks, concepts and relations that make up the FILET. In §7.3 we draw conclusions on the case studies at the aggregate level and focus on the concepts and relations between the building blocks

76 For an elaborate explanation of the concepts within the FILET see Chapter 2.

themselves. For the exploration of the FILET we analysed interactive learning in nutrigenomics consortia. To do this we first took a closer look at nutrigenomics (§7.2).

## 7.2 Nutrigenomics

For our research we wanted to explore the FILET in an emerging technology, and it should also be possible to explore interactive learning between stakeholders within that emerging technology. Therefore, we first had to establish whether or not nutrigenomics was in fact an emerging technology and whether it was an interesting emerging technology to study. By interesting we mean that science and industry stakeholders focus their attention on the emerging technology indicated by relative numbers of patents and publications (i.e. a hot spot). In technologies that are dependent on a combination of complementary knowledge, these activities might involve interactive learning which is indicated by the presence of co-publications and co-patents. In order to obtain an overview of nutrigenomics, we posed two *sub-questions*:

4. *What is nutrigenomics and what are the expectations surrounding nutrigenomics?*
5. *Is the emerging technology of nutrigenomics a hot spot?*

Nutrigenomics is an emerging technology because it has the three characteristics which are typical of an emerging technology:

- There is no dominant design or definition of the technology. For our research we defined nutrigenomics as: research into the relationship between genomes, nutrition and disease (risk) and the future applications that might result from that research.
- While there are no commercially available applications derived from the emerging technology as yet, there are high expectations for future applications. Expected applications resulting from nutrigenomics research are functional foods, nutrigenomics research as a service innovation to substantiate hard claims for functional foods based on scientific evidence, and nutrigenomics tests and dietary advice. These applications could lead to opportunities for preventing and treating nutrition-related, genetically predisposed diseases like the Metabolic Syndrome.
- There is a perceptible increase in linkages between stakeholders in emerging technologies. For nutrigenomics, complementary stakeholders have initiated the formation of consortia in which they collaborate in nutrigenomics research.

Analysis of patents and publications shows that nutrigenomics is a hot spot that attracts a great deal more attention than other fields of technology (expressed in the relative growth in number of patents). The presence of co-publications and co-patents indicates collaboration and interactive learning within the emerging technology of nutrigenomics.

Since nutrigenomics is an emerging technology and a hot spot, it is interesting to explore the FILET within this emerging technology. We performed an exploration of the FILET in two nutrigenomics consortia selected from a list of eight consortia using specific selection criteria (i.e. similarity, interactive learning outcome, nutrigenomics as the core business, and availability and accessibility of empirical data (§4.5)). In the next section we draw conclusions based on these case studies at a more aggregate level.

## 7.3 Exploration of the FILET in nutrigenomics consortia

For the exploration of the FILET in the case studies we formulated three sub-questions:

6. *What was the interactive learning outcome of the consortium?*
7. *How was the interactive learning outcome of the consortium influenced by the elements of the interactive learning process?*
8. *How were the elements of the interactive learning process influenced by the conditions for interactive learning?*

Interactive learning is a process with an outcome; both being closely related to each other. For example, a shared vision is co-constructed by the stakeholders at the beginning of a collaboraion. During the research conducted within the consortium the extent to which the stakeholders are able to realise their co-constructed shared vision becomes clear. In line with the approach taken to our research into interactive learning as discussed in Chapter 4 we will first take a look at the interactive learning outcome (§7.3.1). We then focus on the interactive learning process and *how* that process influenced the interactive learning outcome (§7.3.2). Finally we turn to the conditions for interactive learning and *how* they influenced the elements of the interactive learning process (§7.3.3). In doing so we deal with the three building blocks of the FILET and the relations between them. The major conclusions of the case studies are summarised in §7.3.4.

### 7.3.1 Interactive learning outcome

The *interactive learning outcome* is the outcome of the interactive learning process within the nutrigenomics consortia. The interactive learning outcome is divided into *interactive scientific knowledge outcome* and the *realisation of the shared vision*. In this section we describe the results of the two case studies as far as these two elements of the interactive learning outcome are concerned. The influence of the interactive learning process on the interactive learning outcome is analysed in the next section (§7.3.2).

#### *Interactive scientific knowledge outcome*

The *interactive scientific knowledge outcome* is indicated by (co-)publications, (co-) patents, applications, standards (codified) and an increase in tacit know-how, expertise and problem solving capabilities[77].

The *interactive scientific knowledge outcome* of the Dutch Nutrigenomics Consortium (DNC) and German Competence Network Metabolic Syndrome (CMS) was perceptible in (co-)publications and standards (codified) and in an increase in tacit know-how, expertise and problem solving capabilities. Co-publications are a widely accepted indicator for interactive learning because they can only be written through the interaction of and learning between multiple stakeholders. Among the case studies there were also some 'non-co-authored' publications that were dependent on the interactive learning process between the stakeholders because, according to the stakeholders that were interviewed, the exchange of (tacit) knowledge through

77 For the operationalisation of all concepts see Table 8.

the collaboration was indispensable to write these articles: the interactions allowed the stakeholders to absorb new knowledge which they could then interweave into their articles. Looking at the content of the scientific articles, the articles of the DNC consortium report on gene-gene and gene-nutrient interactions related to metabolic stress. The articles also refer to the tools that were used within the DNC for nutrigenomics research and that can be used for (future) nutrigenomics research. In general terms, the scientific articles of the CMS describe the relation between candidate genes and hypertension, cardio-vascular disease, cholesterol and obesity. The scientific findings in the CMS articles set out the difficulties surrounding nutrigenomics research. Often multiple genes and gene-gene interactions are involved in pathways that may lead up to a disease and contribute to the Metabolic Syndrome.

Standardisation of the exchange of research data, as observed in the DNC consortium, is a codified outcome of (tacit) knowledge exchange during interactive learning processes between the stakeholders. In the early days of the DNC, several stakeholders had their own method of reporting and storing empirical data. This made it difficult for other stakeholders to interpret and use these data. Therefore, arrangements were made to standardise the output so that all stakeholders would be able to work with the data. In the tacit dimension of the interactive scientific knowledge outcome the stakeholders showed to have gained know-how, expertise and problem-solving capabilities resulting from the interactive learning process. Through interaction with other stakeholders it became possible to acquire know-how and expertise on new, complementary knowledge fields and technologies. These interactions also enabled stakeholders to solve the problems they encountered during their research. For example, in the CMS case Dife gained know-how and expertise regarding SNPs analysis methods through discussions on methodological and technological issues with the Max-Planck Institute (specialist in this method). The Max-Planck Institute transferred this method to the University Hospital of Münster which encountered some problems with the new technology. The University Hospital of Münster was able to overcome these problems through a researcher exchange programme between the two institutes and thus gained knowledge and expertise.

To conclude, scientific knowledge outcomes based on interactive learning can be observed in both consortia.

#### *Realisation of the shared vision*

The *realisation of the shared vision* captures the co-construction of a shared vision by the stakeholders at the beginning of the collaboration and the extent to which the stakeholders were able to realise this shared vision at the end of the consortium period. The shared vision encompasses i) a perceived problem, ii) the goal the stakeholders want to achieve, iii) the objectives within this goal, and iv) the approach taken to achieve these objectives. For example, the problem might be concerned with a nutrition-related genetically predisposed disease and the goal of the consortium might be to find a solution to the problem. The objectives that the consortium set itself contribute to the fulfilment of the goal. Therefore an approach might be taken in the form of a division of labour/research among the stakeholders (e.g. research strands or work packages). In this section we present the shared vision that was co-constructed at the beginning of the collaboration and the extent to which this vision was realised

at the end of the consortium period. How the co-construction and realisation were influenced by the interactive learning process is discussed in §7.3.2.

The co-constructed shared visions of the consortia focused on a perceived major health care issue (i.e. obesity for the DNC and hypertension for the CMS consortium) and the overarching goal of the consortia was to find a solution to these problems with the help of nutrigenomics research. For both consortia the objectives became to 1) gain scientific insights and 2) successively develop new applications on the basis of this knowledge (e.g. novel food components for the DNC and patient therapies for the CMS). The shared visions were co-constructed at the start of the consortia. In the DNC case the stakeholders co-constructed an 'integrated' shared vision and in the CMS case the co-constructed shared vision can be regarded as an 'umbrella' that encompassed the individual visions of the stakeholders. At the beginning of the DNC the stakeholders had different individual visions that were related to the research expertise and product portfolio of the stakeholders. During the formation of the DNC these individual visions were integrated into one shared vision, which was to find a solution to the metabolic syndrome. This integration of individual visions is represented by the approach that consisted of interrelated work packages. In the DNC stakeholders could exacerbate on their specific research expertise within separated work packages. These work packages were closely related to each other and the integration of the resulting knowledge could contribute to the fulfilment of the overarching goal. Therefore the research was coordinated and integrated though a so-called 'integrating' work package. In the CMS case the major objective of the individual stakeholders was to refine the research methods they normally worked with. The combination of these objectives was expected to contribute to the overarching goal of the CMS; i.e. to decrease the prevalence of hypertension in Germany. The shared vision of the CMS acted as an umbrella under which the individual stakeholders could fulfil their individual visions. This was also visible in the approach of the CMS that consisted of relatively independent research strands. The knowledge that resulted from the individual research strands was transferred to and bundled by the prime mover, but feedback of the combined knowledge to the other stakeholders was lacking.

New knowledge was created, exchanged and combined during the research conducted within the consortia. Through the resulting scientific insights it became evident to the stakeholders that gene-gene and gene-nutrient interactions are so complex that more research would be needed to obtain sufficient insight into these interactions before applications could be realised. Due to this insight into the complexity of nutrigenomics, the stakeholders were only able to *realise* the scientific objective of their shared vision (i.e. to gain an insight into gene-gene and gene-nutrient interactions). Transformation of this knowledge into applications had to be postponed. As such, the interactive learning process within the consortia led to a more realistic shared vision. The individual stakeholders' visions were related to their expertise and know-how. Since they made use of research methods they were specialised in, they were able to fulfil their individual visions and thus increase their expertise on these methods. In the DNC case the companies involved might possibly have been disappointed about the absence of developed applications. Nevertheless, they had invested primarily in the

consortium in order to gain access to new knowledge and increase their absorptive capacity.

***In summary***

The interactive learning outcome of the consortia is summarised in Table 13. The *interactive scientific knowledge outcome* of the nutrigenomics consortia was evident in (co-)publications and standards (all codified), and in an increase in tacit knowledge in the form of know-how, expertise and problem-solving capabilities.

The *shared visions* that were co-constructed at the beginning of the consortia were partly realised. Through the scientific research conducted within the consortium and the resulting *interactive scientific knowledge outcome* it became evident that nutrigenomics is highly complex and more nutrigenomics research is needed to fully understand the intricate relationship between the genome and nutrition. Consequently the stakeholders could only realise the first objective of the shared visions they had co-constructed at the beginning of the collaboration.

### 7.3.2 Interactive learning process

In the previous section we gave a short description of the interactive learning outcome of the consortia. This description provides the starting point for the analysis of the interactive learning process. In this section we analyse *how* the interactive learning

**Table 13** The interactive learning outcome of the DNC and CMS

| | DNC | CMS |
|---|---|---|
| Scientific knowledge outcome | • 10 publications, 1 WCFS/CMSB co-publication, 3 WCFS co-publications, 2 CMSB co-publications. Reported findings contributed to the realisation of the shared vision<br>• standardisation of data storage and research methods<br>• increase in tacit knowledge; e.g. know-how and expertise on data storage and retrieval (problem-solving regarding incompatible and incomparable data) | • 28 publications, no co-publications. Publications partly dependent on interactive learning. Reported findings contributed to the realisation of the shared vision<br>• increase in tacit knowledge; e.g. know-how, expertise and problem-solving capabilities regarding SNPs analysis methods |
| Realisation of shared vision | • perceived problem: obesity<br>• common goal: to understand processes underlying metabolic stress and find a treatment<br>• objectives:<br>1. to increase understanding of the events unfolding during metabolic stress and<br>2. *develop novel food components [not realised]*<br>• Approach: 6 interrelated work packages and 1 integrative work package | • perceived problem: prevalence of hypertension in Germany<br>• common goal: to find additional treatment for hypertension through nutrigenomics<br>• objectives:<br>1. to increase the understanding of gen-polymorphisms in relation to hypertension and<br>2. *the application of this gained insight for patient therapy [not realised]*<br>• Approach: research strands, accumulation of knowledge by prime mover |

process influenced the interactive learning outcome. Hereto the impact of the four main elements of the interactive learning process (i.e. *prime mover, network formation, knowledge flows,* and *intermediary*) on the two elements of the learning outcome is discussed.

### *Prime mover*

The *prime mover* is the first to take the initiative for network formation. Unilever took the initiative to form the DNC consortium. In the CMS case a professor of the Charité-Universitätsmedizin Berlin assumed the role of prime mover. Both prime movers were triggered by a sense of urgency, being aware of the urgent need to solve a health care problem and recognising the opportunities the emerging technology of nutrigenomics could provide to gain new insights and applications for addressing these health care problems (i.e. obesity in the DNC and hypertension in the CMS). From this point on the prime mover started to form a vision regarding the goal and objectives that could be achieved through a consortium. The prime movers were aware of the dependency on other stakeholders regarding the complementary knowledge that was necessary for them to reach their goal and also the need for resources (e.g. research facilities and funding). For example, in the DNC case, prime mover Unilever had a history in nutrition research and food production. Since nutrigenomics research also requires expertise in genomics, collaboration had to be sought with stakeholders involved in genomics research. Collaboration with these stakeholders would also provide access to the research facilities required to perform research. In the CMS case the Charité-Universitätsmedizin Berlin was specialised in hypertension and aware of the high prevalence of the disease in Germany. Nutrigenomics research could provide new insights into this disease and lead to options for treatment and prevention. In order to gain these insights the prime mover realised the need to cooperate with stakeholders who were familiar with both fundamental and health care-related genomics research.

This observed dependency on complementary stakeholders stimulated the prime movers in the DNC and CMS cases to start forming networks. This network formation was an essential precondition for interactive learning in nutrigenomics that was necessary to obtain the desired results. To summarise, network formation is essential to realise the research goals and a knowledgeable prime mover is crucial in establishing these networks.

### *Network formation*

*Network formation* is indicated by an increase in number of stakeholders, linkages and contact between them. For the formation of the DNC consortium we found that Unilever contacted a large nutrition-based research collaboration (Wageningen Centre for Food Sciences) and a genomics research collaboration (Centre for Medical Systems Biology) through which the network could gain access to the complementary knowledge required for nutrigenomics research on metabolic stress. As such, a growing number of stakeholders became involved and started to interact. In the CMS consortium the prime mover from Charité-Universitätsmedizin Berlin contacted stakeholders specialised in SNPs analysis methods and polygenic mouse models that were complementary to her expertise on hypertension. The network formation resulted in a collaboration of stakeholders that could exchange complementary knowledge and research facilities for nutrigenomics research that was necessary to

generate insights (and if possible, applications) that might contribute towards solving nutrition related genetically predisposed diseases.

The shared vision of the consortia was co-constructed by the stakeholders during the network formation. The prime mover took the lead and his/her need for complementary knowledge was the motive to stimulate and convince complementary stakeholders to take part in the consortia. During the network formation the shared vision was co-constructed further. In the DNC case the individual visions of the stakeholders were integrated into one overall shared vision with the help of an intermediary. For the research institutes the individual visions were related to their research expertise, and for the companies the individual visions were based on the specific product portfolios (e.g. Campina was interested in butter and Unilever in margarine). The individual visions were integrated into one shared vision. This integration was also visible in the interrelated work packages of the DNC[78]. A stakeholder whose expertise corresponded with the work package topic headed the work package. Within the work packages different stakeholders collaborated. The work packages were integrated with the help of a so-called integrating work package that entailed the coordination of mouse/human studies and the standardisation of data. The work packages had a twofold purpose: 1) pursuing the individual visions of the stakeholders in the work packages in which they had the lead through collaboration with other stakeholders within that work package, and 2) contributing to the overarching shared vision through the integrating work package. In the CMS case the vision of the prime mover was to use nutrigenomics research to find treatments for hypertension. The stakeholders that were contacted by the prime mover had their own individual visions, namely the application and development of their research methods (e.g. the Max-Planck Institute's SNPs analysis method and the Dife's polygenic mouse studies). The pursuit of these individual visions could contributed to the prime mover's vision. Therefore, the prime mover's vision was adopted as the shared vision, which can be seen as an umbrella that encompassed the individual visions. This became also visible in the three relatively separated research strands that were bundled by the prime mover. In the CMS case the stakeholders were more focused on the pursuit of their individual vision than in the DNC case, where stakeholders had co-constructed a shared vision with the help of an intermediary.

***Knowledge flows***

The *knowledge flows* contain the knowledge that is created, exchanged and combined by the stakeholders in the consortia. In the DNC case, the standardisation of methods, experiments and databases can be mentioned as typical examples of interactive learning. This standardisation was necessary for the exchange and interpretation of research data by stakeholders with a nutrition and genetics background. Prior to collaboration in the DNC the stakeholders had used their own 'standards', and consequently data of one stakeholder could not be used for analysis and comparison by another. The standards were a direct result of the interaction and exchange of tacit knowledge between the stakeholders in the consortium. In the CMS case, the Max-Planck Institute developed and improved the SNPs analysis methods that could be

78 For a detailed overview of the DNC work packages see Figure 28, p.106.

used for screening patient material for candidate genes for hypertension. This method was transferred to the University Hospital of Münster where it could be used for screening purposes. This technology transfer was arranged through the exchange of researchers between the institutes. Dife performed polygenic mouse studies that resulted in 3-4 candidate genes that were transferred to the University Hospital of Münster. The results of the polygenic mouse studies could be used by the University Hospital of Münster to screen patient cohorts through the SNPs analysis methods provided by the Max-Planck Institute. The Max-Planck Institute and Dife discussed technical and methodological issues related to the SNPs analysis methods. This can be seen as a typical example of tacit knowledge exchange and interactive learning.

The *knowledge flows* between the stakeholders accumulated in an increase of know-how, expertise and problem-solving capabilities (as e.g. the case with the SNPs analysis methods) and became (partly) codified in scientific articles.

During the scientific research conducted in the consortia the stakeholders found that nutrigenomics research is highly complex and that many scientific questions still had to be answered before concrete applications could be realised. This implied that the stakeholders – in both cases – could only realise the first objective (i.e. deepening scientific insight) of their shared vision. The application of this knowledge into novel food components and patient therapies was apparently too ambitious.

#### *Intermediary*

An *intermediary* is expected to bridge a potential knowledge gap by 'translating' knowledge from one stakeholder to another. In our research the function of an intermediary was perceived originally as a specific stakeholder with the role of translator.

For the DNC case we already mentioned the intermediary that integrated the individual visions during the network formation. Two additional intermediary functions became discernible during the actual research that was conducted in the DNC. First, in so called 'exemplification' projects (i.e. explorative demonstration projects) TNO 'translated' scientific knowledge into knowledge that could be used by various stakeholders for the development of future applications. Second, we observed 'boundary objects' (e.g. mouse models) that acted as a common point of reference for heterogeneous stakeholders and enabled them to bridge the gap between their different fields of knowledge. This finding in the DNC case indicates that the concept of an intermediary should not necessarily be limited to the specific function of a stakeholder, but the intermediary function might also apply to 'objects'. As becomes clear from these examples, specific objects can play an important role as 'translator' between researchers in a consortium.

As mentioned above, in the CMS case there was no specific actor that assumed the role of intermediary during the network formation. While stakeholders in the CMS had their own individual visions they independently contributed to the overall vision. In other words, there was no need for an intermediary to translate the individual visions into a single vision because the shared vision acted as an umbrella that encompassed the individual visions. Also during the actual research conducted within the CMS there was no stakeholder that assumed the specific role of an intermediary. The stakeholders within the CMS were from different scientific backgrounds and consequently had dissimilar expertise regarding methods of research. In order

to overcome potential knowledge gaps between these fields of knowledge, the stakeholders put extra emphasis on explaining research methods that were not familiar to all stakeholders. As such, each stakeholder exchanged his research methods with the other stakeholders without the help of a specific intermediary.

***In summary***

The main elements of the interactive learning process are the prime mover, network formation, knowledge flows and the intermediary. In the case studies we observed a 'sequence of events' in the interactive learning process. First, a network of complementary stakeholders was formed, initiated by the prime mover. During the network formation a shared vision was co-constructed. Second, during research conducted within the consortia knowledge flows between the stakeholders resulted in interactive learning and increased scientific insight. The exchange of knowledge was sometimes facilitated by an intermediary, e.g. in the DNC case by TNO in so-called exemplification projects, and through mouse models which acted as a shared frame of reference for the stakeholders. The scientific insights determined the extent to which the stakeholders could realise the shared vision.

The prime movers initiated the formation of networks in the emerging technology of nutrigenomics on the basis of a sense of urgency (i.e. the combination of health care issues and new opportunities through nutrigenomics) and a perceived mutual dependency among stakeholders on complementary knowledge and resources. During the network formation the stakeholders co-constructed a shared vision. In the DNC case the individual visions were integrated into a shared vision with the help of an intermediary by designing interrelated work packages. Individual work packages corresponded with the expertise of the leading stakeholders, and the work packages were subsequently integrated in the 'integrating' work package. The network formation of complementary stakeholders from nutrition and genomics fields of knowledge was necessary to gain additional scientific insight into nutrigenomics. In the CMS case the shared vision was an umbrella that encompassed the stakeholders' individual visions.

The knowledge flows between the stakeholders resulted in an increase in interactive scientific knowledge outcome, in scientific articles, and tacit know-how and expertise. During the research within the DNC, the mouse models and TNO fulfilled an important role as the intermediary in this interactive learning process by functioning as a shared frame of reference, and the facilitation of exemplification projects, respectively. Ultimately however, the stakeholders were only able to realise the first objective of the shared vision. During the lifetime of the consortia it became clear that it was still too early to transform these scientific results into practical applications. To do this, more scientific questions regarding the complex relation between the genome, nutrition and disease have to be answered.

### 7.3.3 Interactive learning conditions

In this section we look at the conditions for interactive learning and how they influenced the elements of the interactive learning process. These conditions are the *geographical, cognitive, regulatory, cultural, social* and *organisational proximity*.

### *Geographical proximity*

Geographical proximity is indicated by a geographical agglomeration of stakeholders. It was assumed that agglomerations enable face-to-face interaction, which in turn facilitate the exchange of complex and tacit knowledge. In both the DNC and CMS cases the stakeholders were geographically concentrated in the Netherlands (with centres of gravity in the Wageningen Food Valley and Leiden) and in the Berlin/Brandenburg region of Germany respectively.

These agglomerations had a positive influence on the *prime mover* and the *network formation* because they enabled face-to-face meetings during which complex issues could be discussed and arranged. For instance, in the first meetings of the DNC consortium the Intellectual Property Rights (IPR) and Non-Disclosure Agreements (NDA) that would become part of the mutual agreement were discussed. Since not all DNC stakeholders were familiar with each other and the CMS stakeholders had no shared history, these initial meetings were also used by stakeholders to assess whether they could learn from one another and whether there was a basis for trust. Face-to-face interaction is clearly prerequisite for building up trust during the network formation.

During the actual research conducted within the consortia *temporary geographical proximity* appeared to be sufficient to facilitate *knowledge flows* between stakeholders. Occasionally stakeholders met face-to-face during (in)formal meetings. In the CMS consortium researchers of the organisations that were involved in the transfer of the SNPs analysis methods stayed as guests at each other's institutes in order to transfer and absorb knowledge about this method. These 'guest researchers' are a clear example of the value of temporary geographical proximity.

In conclusion, geographical proximity facilitates the activities of the prime mover to start up the network and create trust between actors with no shared history. As such, geographical proximity is very important for the emergence of the network. Temporary geographical proximity assists the functioning of the network by facilitating the exchange of tacit knowledge about the use and/or relevance of the transferred knowledge.

### *Cognitive proximity*

Cognitive proximity is operationalised in terms of technological foci, co-citations and cross-citations and the journals stakeholders publish in. It was assumed that the *cognitive distance* between stakeholders influences the interactive learning process in several ways. First, it was assumed that the prime mover and the stakeholders within the network formation would search for stakeholders with complementary knowledge that could 'understand' each other, if necessary with the help of an intermediary. The second assumption was that interaction between actors at a cognitive distance would lead to combined complementary knowledge about (in our research) nutrition and genomics. The cognitive distance should not be too great and a certain amount of absorptive capacity is needed in order to bridge a potential knowledge gap. In the DNC and CMS consortia the absence of cross-citations and the limited number of co-citations can be interpreted as a lack of cognitive proximity between the stakeholders.

In the DNC case, prime mover Unilever had a background in nutrition research and production. For the performance of nutrigenomics research Unilever first contacted the WCFS for their expertise in nutrition research. Since the WCFS was

also specialised in nutrition research there was no cognitive distance between the WCFS and Unilever. But genomics expertise would also be needed for nutrigenomics research. In order to incorporate complementary knowledge about genomics the CMSB was approached. Despite the cognitive distance, the stakeholders were able to 'understand' each other during the network formation without the help of an intermediary[79]. During the actual research within the DNC, objects like mouse models functioned as 'boundary objects' that played a role as a common point of reference for stakeholders from genomics and nutrition, and helped the stakeholders to 'understand' each other's research. This mutual understanding led to the generation of new nutrigenomics knowledge, for which knowledge from nutrition and genomics had to be combined. To this end these mouse models played a role as an intermediary.

In the CMS case, the prime mover contacted stakeholders who were able to contribute complementary knowledge on the relationship between nutrigenomics and hypertension. During the network formation within the CMS we observed that the stakeholders assessed whether they would be able to learn from each other, bridging the gap between the stakeholders technological foci. Both during the network formation and the actual research within the CMS consortium were the stakeholders able to understand and learn from each other without the help of an intermediary. For example, the Max-Planck Institute's expertise on SNPs analysis methods was needed by the University Hospital of Münster. The existence of the consortium created the context within which the Max-Planck Institute was both able and willing to exchange knowledge about this method with Münster.

To conclude, there will be a cognitive distance when combined complementary knowledge is needed for interactive learning. Sometimes actors can bridge this gap themselves. Sometimes an intermediary is necessary for translation and further explanation. Such an intermediary may take the form of an individual/organisation but can also be a boundary object that acts as a joint point of reference.

***Regulatory proximity***

Regulatory proximity is subdivided into regulatory proximity at the *macro level* and regulatory proximity at the *meso level*.

Regulatory proximity at the *macro level* encompasses national and international regulations that reduce uncertainty and government budgets for funding research. It was assumed that regulatory proximity at the macro level stimulates the prime mover and network formation. First, government funding was a necessary condition for the network formation of both consortia because nutrigenomics research is so risky and expensive that individual stakeholders and even stakeholder consortia hesitate to invest. Substantial research in such high-risk fields will not take off without government support. Government funding in the Netherlands (DNC case) was made available through the National Genomics Initiative and in Germany (CMS case) through the Verein zur Förderung der Nutrigenomforschung. Together with the matching funds of the stakeholders concerned, the government funding enabled nutrigenomics research to be performed within the consortia. Second, rules and regulations at the macro level can also reduce uncertainty for the stakeholders because they can help to create a level

79 During the network formation of the DNC an intermediary did help with to co-construct a shared vision.

playing field, which is essential for fair and open competition, or can help to create a future market. Regarding the latter, EU legislation (i.e. (COM (2003) 424)[80]) creates a protected market space for functional foods based on solid claims. These claims must be based on scientific evidence, thus making it worthwhile to invest in nutrigenomics. This aforementioned EU legislation will provide more certainty in terms of future return on investment. Clearly, the existence of this legislation provided an extra stimulus for the prime mover to start the network formation, and a stimulus for the stakeholders to collaborate and invest in nutrigenomics research.

Regulatory proximity at the *meso level* (indicated by a mutual agreement between the stakeholders in the consortium) was assumed to have a positive influence on the knowledge flows because mutual agreements prevent unwanted spill-overs. During the network formation in both consortia mutual agreements were drawn up to regulate IPR and NDA issues. Within the DNC consortium the stakeholders agreed on a patent mechanism that satisfied both the WCFS and the CMSB. As a consequence, the stakeholders knew what would happen to the knowledge they contributed to the consortium, and that they would be credited for their contribution. The stakeholders also agreed not to perform similar research outside the DNC. Thanks to this agreement the stakeholders shared their knowledge freely within the consortium. Unambiguous arrangements were also drawn up in the CMS case about who would be involved in publications and patents.

To conclude, governments provided funding for nutrigenomics research and a favourable regulatory framework in terms of protected spaces and some guarantees for a future market. During formation of the network the stakeholders drew up arrangements on IPR and NDA issues in mutual agreements which facilitated the free flow of knowledge between the stakeholders (i.e. meso level).

***Cultural proximity***

Cultural proximity refers to the underlying incentive structure and is reflected in the type of organisation. We distinguished two types of organisations and associated incentive structures: universities/research institutes that focus on publications, and companies that focus on patents. It was assumed that the prime mover and the stakeholders involved in the network formation would look for stakeholders with the same underlying incentive structure given that a difference in incentive structure could hinder the knowledge flows between the stakeholders.

The DNC was a collaboration of research institutes and companies. Normally these organisations work under different incentive structures. Nevertheless they decided to collaborate in the DNC because the research institutes were also familiar with patenting[81]. For the companies the research collaboration was a way to be involved in research that could provide new business opportunities. In the CMS consortium only

80 NB This proposal was made in 2003 and was accepted by the EU council on 12 October 2006. Since then it is known as EU Regulation 1924/2006 (see http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:EN:PDF). At the time of the existence of the DNC and CMS the proposal still had to be rectified by all EU Member States.

81 The research institutes within the WCFS and CMSB were already used to filing patent applications for promising scientific findings that could have economic value.

research institutes participated in the actual research[82], which would indicate that the consortium would focus on scientific publications. However, in the CMS consortium the stakeholders appeared to have a dual focus; being both interested in publications and patents. This dual focus appeared to be typical of the German research system in which most research institutes are supposed to generate income from various types of sources, including application-oriented research funding (with patents as a performance indicator).

To conclude, all stakeholders in the nutrigenomics consortia were interested in both publications and patents and these interests were not in conflict with each other.

***Social proximity***

Social proximity is the presence of trust, which is indicated by a shared history and access to each other's research facilities and data bases. Trust facilitates the exchange of knowledge – and therefore supports the activities of the prime mover, network formation and knowledge flows. Based on the history Unilever shared with the WCFS, *prime mover* Unilever first contacted the WCFS for collaboration in the DNC. The CMSB was contacted at a later date for their complementary knowledge on genomics research. Although the stakeholders trusted each other during the research performed within the DNC, they also signed a mutual agreement. The mutual agreement could prevent unwanted spill-overs in case a 'competitive situation' should arise between the stakeholders. In this way the agreement reinforced the trust between the stakeholders. In the CMS case, only the *prime mover* had a shared history with the other stakeholders. However, the case study showed us that the stakeholders assessed the presence of trust among themselves during the network formation. Temporary geographical proximity played an important role in generating trust. The actual presence of trust between the stakeholders in both consortia is evident from the free access they granted one another to use their research facilities and databases. In the CMS case, researchers and expertise on research methods were exchanged between stakeholders. This trust had a positive influence on the *knowledge flow.*

To conclude, trust can be based on a shared history, or created during face-to face contact among the stakeholders within the context of the consortium. The presence of trust during the research performed in the consortia stimulated the exchange of knowledge, researchers and methods.

***Organisational proximity***

Organisational proximity refers to the organisation and coordination of stakeholders' actions within the consortia. It was assumed that a balance between flexibility and coordination facilitates the 'production' and combination of new knowledge. Knowledge creation on the boundaries of complementary fields of knowledge requires coordination. Besides the coordination of knowledge creation, innovation is also dependent on the autonomy of the individual stakeholders. Stakeholders should be able to pursue their quest for knowledge unhindered by too restrictive settings, because unexpected insights and serendipity might lead to the need to exploit new possibilities instead of following fixed (or even outdated) working packages and

82 Because the participation of a company was a requirement for funding, a company was formally involved in the CMS but was not involved in the actual research.

routines. In the DNC case there was a balance between flexibility and coordination, but coordination was lacking in the CMS.

During the network formation of the DNC, organisation of the research was realised by defining six interrelated work packages and one integrating work package. The stakeholders had the flexibility within each separate work package to perform their research according to their own visions, insights and approaches. The research that was performed in the six work packages was coordinated through the so-called integrating work package. As such, both flexibility and coordination were present within the DNC and this allowed the free search for new knowledge in nutrition and genomics, and the combination of the complementary knowledge flows into nutrigenomics knowledge. Within the CMS case, the individual stakeholders all had their own research strands. Coordination in the CMS was evidently lacking because there was no feedback from the prime mover in the University Hospital of Münster – the location where all knowledge accumulated – to the other stakeholders. For example, Dife performed polygenetic mouse studies in order to identify candidate genes. The identified genes were then transferred to the University Hospital of Münster for further analyses of their role in hypertension, but there was no interaction regarding the outcomes of those analyses.

To conclude, the organisational proximity was 'set' during the network formation of the consortia. In the DNC case the stakeholders' actions stimulated the search for new knowledge in individual work packages, and attempted to combine the resulting complementary knowledge flows in an integrating work package. Coordination was lacking in the CMS. The differences in organisational proximity between the DNC and CMS might be explained from the difference in how the shared vision was co-constructed. In the DNC the stakeholders arrived at a shared vision in which the individual visions were integrated. The shared vision of the CMS was merely an umbrella for the individual visions of the stakeholders involved. The latter way of organising research did not stimulate interaction as much as was the case in the 'interrelated work packages model' of the DNC.

***In summary***

*Geographical proximity* and *cognitive distance* had a positive influence on the prime mover, network formation and the knowledge flows. *Regulatory proximity at the macro level* (funding, EU regulations) positively influenced the prime mover and the network formation, and *regulatory proximity at the meso level* had a positive influence on the knowledge flows. *Organisational* and *social proximity* had a positive effect on the knowledge flows. For *cultural proximity* we have to conclude that, despite the cultural differences between research institutes and firms, the stakeholders did have a similar focus on publications and patents.

*Geographical, cognitive, cultural* and *regulatory proximity at the macro level* were already determined before collaboration in the consortia started. Regulatory *proximity at the meso level* and *organisational proximity* were shaped during the first phases of the formation process. Trust (i.e. *social proximity*) was already present between stakeholders that had a shared history. However, we observed that the stakeholders with no shared history assessed the presence of trust during network formation by organising face-to-face meetings within the context of the consortium.

### 7.3.4 Major conclusions of the case studies

The major conclusions resulting from the exploration of the FILET in the nutrigenomics case studies are:

- Government funding was a *necessary pre-condition* for the nutrigenomics consortia. Without the availability of government funding the stakeholders would not have embarked on the long term, risky and expensive nutrigenomics research.
- The case studies showed a 'sequence of events' in interactive learning. First, a *formative stage* in which the prime mover contacts complementary stakeholders and the network is formed. In the formative stage a shared vision is co-constructed by the stakeholders. Second, a *research stage* in which the scientific research is performed. Knowledge between the stakeholders is exchanged and combined in the research stage. This interactive learning results in interactive scientific knowledge outcome as expressed in the scientific articles and in an increase of tacit knowledge. On the basis of these scientific insights the stakeholders can determine to what extent it is realistic to realise the shared vision they co-constructed at the beginning of the collaboration.
- Some dimensions of proximity that influence the interactive learning process are not fully determined at the beginning of the collaboration and are further defined during the formative stage:
  - *Social proximity* between stakeholders is present if they have a shared history. In the case studies not all stakeholders had a shared history and those stakeholders used the first meetings during the formative stage of the consortium to assess whether there was trust between them.
  - *Regulatory proximity* at the meso level is indicated by mutual agreements settling IPR and NDA issues. These mutual agreements are drafted and signed during the formative stage before the actual research collaboration between the stakeholders begins.
  - During the formative stage *the stakeholders* agree upon how their research will be organised within the consortium. This arrangement determines the *organisational proximity*.
- In the *research stage* we observed that objects like mouse models also fulfilled an intermediary function. These objects acted as a common point of reference that helped the heterogeneous stakeholders to cross the boundaries between their knowledge fields (i.e. nutrition and genetics). Thus, the intermediary function can be fulfilled not only by a stakeholder, but also by 'boundary objects'.

These major conclusions are incorporated in an adapted visual representation of the FILET (Figure 38).

In this section we summarised the major conclusions resulting from our research. In the next section we discuss the research design and the internal and external validity of the findings of our research.

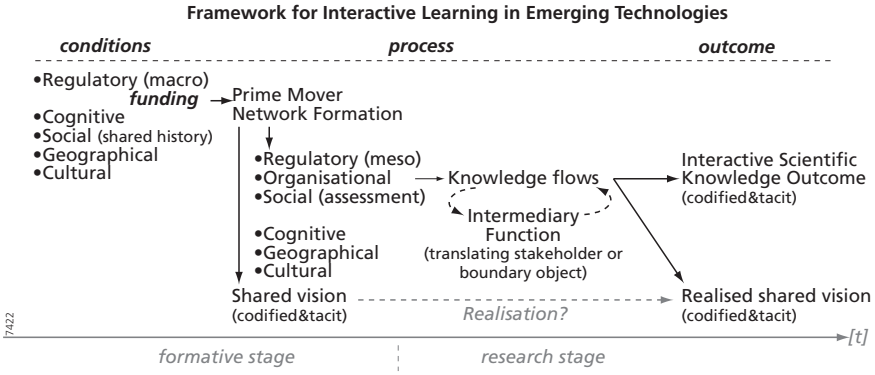



**Figure 38** FILET based on major conclusions of case studies

## 7.4 Discussion

In this section we first discuss the research design (§7.4.1): we discuss the advantages and disadvantages of the case study method, the operationalisation of concepts, and the scientometrics analysis as performed in §3.5. Next we discuss the case study findings (§7.4.2). Finally, we assess the internal (§7.4.3) and external validity (§7.4.4) of the developed FILET.

### 7.4.1 Research design

The aim of our research was to understand interactive learning in emerging technologies. Therefore we developed a framework linking outcome, process and conditions of interactive learning (FILET). The FILET aimed to describe the real-life phenomenon of interactive learning and thus the case study was the preferred research method for exploration of the FILET. The case studies were selected through theoretical sampling. Using a specific set of criteria the following cases were studied: the Dutch Nutrigenomics Consortium (DNC) and the German Competence Network Metabolic Syndrome (CMS). The case studies provided detailed insight into the interactive learning process, and shed light on the relationship between knowledge flows, the interactive scientific knowledge outcome and the co-construction and realisation of a shared vision. The interviews with stakeholders provided insight into the increase of their (tacit) knowledge through interactive learning with other stakeholders in the consortium. As such, the case study method helped us to open up the black box of interactive learning a bit further. This is advantageous when compared to other research that primarily focuses on the codified outcome of the interactive learning process. The disadvantage of case studies is that they are very time-consuming and encompass labour intensive steps like arranging meetings with stakeholders, retrieving grey literature from stakeholders (e.g. CMS final report or an informative input document for the DNC website), holding interviews, making transcripts of these interviews, obtaining authorisation for the transcripts, coding and analysing the transcripts, and constructing a case history based on all sources of evidence.

The *operationalisation* of the theoretical concepts in observable variables used in the case studies was based on literature dealing with these concepts. From this literature we selected a set of indicators. Here we reflect on two of them:

- Regarding the use of patents, applications, and publications we have to discuss two issues. First, within the case studies we found no patents or applications. This is related to the science-based character of the consortia which had not yet resulted in patents and applications. However, we would not leave out these indicators from the operationalisation table because other consortia in emerging technologies might be closer to application. Second, when we operationalised the interactive learning outcome (see §4.7.1) we argued that for consortia it is sometimes difficult to identify which articles, patents and applications are the specific result of interactive learning in the consortia. Consortia often have a complex structure, including different stakeholders, each with their own complex internal structure (e.g. departments, research groups, etc.), numerous research projects and contact with other actors outside the consortium. We used the evaluation reports of the consortia as a starting point for the first assessment of the outcome. As a next step, we checked the consortia websites that also provide information on the outcome. Nevertheless, this approach does not guarantee a complete overview. In the DNC case a patent was reported on the website, but inquiries into this patent showed that it was not a result of research performed within the DNC. This shows that it is important to double-check the reported outcome. Therefore, we discussed the reported outcome with stakeholders during interviews and email conversations.
- There is some discussion on the value or usability of tacit knowledge. Cowan, Foray and David (2000) argued that tacit knowledge represents no economic value since it cannot be traded (like patents for instance) and therefore it cannot be used in standard micro-economic models of human behaviour. According to these authors, this would not be a problem because only a small part of all knowledge is tacit knowledge and therefore can be left out of standard micro-economic models. However, according to Maskell and Malmberg (1999) *"the really valuable knowledge is [..] still at least partially tacit"*. In a direct reaction to Cowan, Foray and David (2000) Johnson, Lorenz and Lundvall (2002) stress the importance of tacit knowledge, because not all knowledge might be possible to codify and some of this tacit knowledge might be crucial for the innovation process. For example, a scientific article does not normally reflect the authors' full know-how that might be crucial for interpretation of the findings. It is even more difficult to codify belief systems, values or norms which are crucial in the co-construction of a shared vision. Thus tacit knowledge is a very significant factor in interactive learning in emerging technologies and therefore the concept of tacit knowledge has to be incorporated into the analysis despite the difficulties regarding the measurement of tacit knowledge. To measure tacit knowledge we held interviews with stakeholders in order to gain insight into the exchange between stakeholders and the accumulation of tacit knowledge (e.g. increase in know-how, expertise and problem-solving abilities). These interviews allowed us to gain insight into the stakeholders' tacit knowledge that was not – yet – codified in e.g. scientific articles.

In Chapter 3 we showed that nutrigenomics meets the three requirements that define an emerging technology: i) the absence of a dominant design or definition and

commercially available applications, ii) uncertainty about future applications and high expectations, and iii) an increase in linkages between stakeholders. The classification of nutrigenomics as an emergent technology was confirmed by the stakeholders involved in nutrigenomics. Additionally, we performed a scientometrics analysis in order to find out whether nutrigenomics was hot spot, i.e. that science and industry are interested in nutrigenomics and that research activities are being performed. The use of patent and publication data for analysis does have some pros and cons, which were mentioned in §3.5.1. Here we address a more fundamental point. In order to become visible as a hot spot, a technology (e.g. nutrigenomics) requires a certain amount of critical mass in terms of patent numbers and publications. This implies that promising developments that have not yet been codified, or are only represented in a few patents or publications, are not identified because they do not stand out against other subfields with a higher number of patents or more publications. Within the emerging technology of nutrigenomics codified results were present that had enough critical mass to become visible as a hot spot.

### 7.4.2 Discussion of case study findings

In the previous section we discussed the advantages and disadvantages of the research design. In this section we discuss specific case study findings that presented us with insights into the interactive learning process. Therefore we discuss cultural and social proximity because the case studies yielded insights that were not expected on the basis of the assumed relation within the FILET.

Stakeholders from science and industry collaborated in the DNC case. As such, it was expected that the consortium would have to deal with two different underlying incentive structures. For science the underlying incentive structure is publishing, and for industry, patenting. In general it was assumed that a difference in incentive structure would impede the free flow of knowledge. In the case studies we found that a difference in underlying incentive structure had no restricting influence on knowledge flows. This can be explained as follows: First, new knowledge often emerges from research institutes and therefore these organisations are a valuable source of new knowledge for companies. Consequently companies are aware that they have to invest in basic research with universities. At the same time, collaboration with research institutes increases the absorptive capacity of companies. Second, driven by the necessity to gather resources for research, universities also try to market their scientific findings through patents. Third, for research institutes collaboration with companies provides access to (additional) resources, such as R&D funding and technical support. Fourth, conflicting situations could be prevented through agreements about publication and patenting set out in the mutual agreements (i.e. regulatory proximity at the meso level).

Here we could ask ourselves the question whether a different interpretation of cultural proximity could or should be used? Cultural proximity was assumed to be related to the proxy of the underlying incentive structure (Ponds, Oort et al. 2007; Ponds 2008). In the DNC case we also observed a difference in management culture between the CMSB and WCFS. This interpretation of culture differs from our operationalisation of cultural proximity. Maybe a different or broader interpretation of

culture might have created a more diverse image of the stakeholders' cultures and the influence of the difference between these cultures on the interactive learning process.

Regarding trust (i.e. social proximity) two findings need further discussion. First, social proximity was indicated by a shared history. The case studies showed that not all stakeholders had a shared history and, as such, trust between these stakeholders was not yet present at the beginning of the collaboration. These stakeholders assessed whether they trusted one another during face-to-face meetings in the early phase of the formation of the consortia. Face-to-face meetings are the richest medium that can be used to exchange knowledge and information (Bongers 2000). At the same time, face-to-face meetings allow the interpretation of non-verbal cues that could be important to build up trust. Second, trust and mutual agreements seem to be related to each other. Trust is a basis to reach mutual agreements and at the same time mutual agreements reinforce trust. For example, the stakeholders in the DNC trusted each other as long as there was no competitive situation. If a competitive situation should arise during the research conducted within the consortium, the stakeholders would fall back on the formal IPR arrangements. Agreements, including agreements on IPR and NDA issues, were drawn up in both consortia.

The case study findings that we discussed above provide starting points for recommendations for further research. These will be presented in §7.5.1. First, we turn to the internal and external validity of our research.

### 7.4.3 Internal validity

Internal validity refers to the usefulness of the concepts and the relationships between the concepts in the FILET to describe and understand interactive learning in emerging technologies.

The FILET we developed consisted of three building blocks: the interactive learning outcome, the interactive learning process and the conditions for interactive learning. Each building block contained concepts that were derived from literature on innovation, interactive learning and proximity. Between the building blocks we proposed relations between the concepts (e.g. the influence of geographical proximity on network formation).

We explored the framework in two case studies of nutrigenomics consortia. Both case studies showed that the concepts and proposed relations between the concepts were useful for describing and analysing the interactive learning process within the consortia. The FILET allowed us to identify the concepts that are part of interactive learning and to assess how these concepts of interactive learning influenced each other within the case studies. At the same time, the use of semi-structured interviews with the stakeholders in the case studies left room for the identification of other factors that might be involved in the interactive learning process, but were not incorporated in the developed FILET. No major additional factors were identified during the exploration of the FILET in the case studies and the interviews. Therefore, based on the results of these two case studies it may be concluded that the FILET constitutes a reasonably complete framework, which makes the FILET an *internally valid* framework for describing interactive learning in the nutrigenomics consortia.

### 7.4.4 External validity

External validity refers to the extent to which the developed framework applies to other situations of interactive learning in emerging technologies.

For exploration of the FILET we turned to the emerging technology of nutrigenomics. Within nutrigenomics interactive learning between complementary stakeholders was localised in nutrigenomics consortia. The most appropriate nutrigenomics consortia were selected from a list of eight nutrigenomics consortia with the help of selection criteria. Subsequently the FILET was explored in the DNC and CMS case. Since the FILET was explored in two nutrigenomics consortia, the possibilities to draw more general conclusions on the basis of these specific cases is somewhat limited. However, due to the demonstrated feasibility of the framework in the case studies it seems likely that the FILET can also be applied in similar cases of interactive learning in stakeholder collaborations in other emerging technologies. Ultimately, the generalisation of the FILET has to be explored through replication logic in other circumstances.

## 7.5 Recommendations

Starting from the development of the FILET, the results of the exploration in the case studies and the discussion, we now formulate recommendations for further research (§7.5.1) for stakeholders (§7.5.2) and policy makers (§7.5.3). For this purpose we formulated a *sub-question* at the beginning of our research:

9. *Which lessons can be drawn for future research on interactive learning in emerging technologies, and which recommendations can be made to stakeholders and policy makers who would like to stimulate interactive learning and innovation in emerging technologies?*

### 7.5.1 For further research

Based on our research and the related discussion (§7.4), we formulate the following recommendations for further research:

- The emerging technology of nutrigenomics is a subfield within genomics. Therefore, studying interactive learning in other emerging genomics fields (e.g. pharmacogenomics) might be useful to improve the external validity of the framework. Application of the FILET in other emerging technologies, such as nanotechnology, gene therapy, stem cell research, or sustainable and renewable energy technologies such as fuel cells could improve the external validity further. *Therefore we recommend further exploration of the FILET in different case studies in the field of emerging technologies.*
- Cultural proximity was indicated by the underlying incentive structure of the stakeholders. As we observed and discussed, in the case studies the stakeholders had a dual focus. In other words: industry as well as science focused both on scientific insights and patents. Further research is recommended to see whether other, more advanced interpretations of cultural proximity yield the same results. *Therefore we recommend research into interactive learning with different interpretations of cultural proximity.* For example, in their study Heinze and Kuhlmann (2008)

take a more elaborate approach on culture. Heinze and Kuhlmann start from the notion that "*the need for effective inter-institutional knowledge flows is of particular importance in emerging domains of research*". Because little is known about the institutional conditions, they investigate a broad set of cultural elements like stereotypes and prejudices, working routines, and interface management (Heinze and Kuhlmann 2008).

- Stakeholders that had no shared history assessed whether they trusted each other during face-to-face meetings. Face-to-face meetings are the richest medium for the exchange of knowledge. Besides verbal statements by stakeholders also non-verbal factors can be assessed that might – subconsciously – play a role in assessing trust (e.g. does someone look trustworthy). These psychological non-verbal factors on the micro level (i.e. between individuals) were not part of our research. For innovation studies it might be interesting to explore the influence of these factors in this crucial phase of the innovation process. *Therefore, we recommend research into psychological non-verbal factors in the interactive learning process, especially regarding the build-up of trust between stakeholders.*
- The case studies indicated that there seems to be a relationship between trust (i.e. social proximity) and agreements (i.e. regulatory proximity at the meso level). The purpose of our research was to improve insight into the interactive learning process and how this process is influenced. Therefore we did not dive deeper into the relations between the different proximities. Other researchers have focused specifically on the relations between specific proximities. For example, Phlippen (2008) refers to "*interaction effects*" between geographical, cognitive and relational proximity[83]. More insight into the interdependency of different dimensions of proximity and their influence on the interactive learning process could present additional insights into interactive learning. *Future research could focus on the relation between dimensions of proximity, how they complement, substitute or succeed one another, and how these relations influence the interactive learning process.*
- In their research on collaboration between French academic organisations and firms Goddard and Isabelle (Goddard and Isabelle 2006) showed that the most frequent outcome of these collaborations are (co-)publications. In our case studies this turned out to be a rather limited indicator because it did not include all interactive learning results. The indicator had a bias towards codified results and undervalued the tacit dimension (e.g. know-how, expertise and problem solving capabilities). Such tacit dimensions often give a better insight into the interactive learning process. Therefore, we not only focused on the output in terms of (codified) publications and patents, but also on the build-up of know-how and expertise, and the ability to solve problems. This approach allowed us to gain a more complete insight into the relation between the interactive learning process and the interactive learning outcome. An anthropological approach (as for example taken by Penders (2008)) in which the researcher participates in nutrigenomics consortia and observes tacit knowledge flows between stakeholders could provide more detailed insights into the relation between the tacit knowledge flows and the increase in know-how and expertise, the problem-solving ability and the impact

83 *"Relational proximity comes very close to the notion of social proximity"* (Phlippen 2008).

of this knowledge on publications. *Therefore, one last recommendation for further research into interactive learning in emerging technologies concerns the use of an anthropological approach in order to gain detailed insights into knowledge flows and an increase in the tacit knowledge of stakeholders.*

### 7.5.2 For stakeholders

In this section we turn to the stakeholders involved in the consortia. The recommendations focus on improving the management of their activities in the consortium.

- In our case studies we found that mutual agreements between the stakeholders in a consortium are an important outcome of the formative stage because they prevent unwanted spill-overs and stimulate knowledge flows between the stakeholders. For instance, the IPR arrangements were a major point of discussion during the formative stage of the DNC. For stakeholders embarking on a collaboration it is not always clear which issues should be on the agenda when discussing the mutual arrangement. Therefore we can recommend the list of the NIH office of the Ombudsman Prenup, which might be used as a checklist for the issues that should be covered in such an agreement (Ledford 2008)[84]:
  - What do we expect to get out of this?
  - Who is going to do what and by when?
  - Who will have access to our data?
  - Who will give public presentations, and how much data will they reveal?
  - How will we assign authorship?
  - How will we decide when to publish?
  - Who owns the intellectual property?
  - Will we share our reagents with other labs?
  - What happens if one of us leaves the project?
  - What happens if one of us wants to form a separate, but related, collaboration with another lab?
- Since not all contingencies in an emerging technology can be foreseen and covered by a mutual agreement, the presence of trust – which stimulates knowledge flows – is also important. One of the major conclusions that resulted from the case studies was that trust between stakeholders is sometimes based on earlier collaborations and is already present before the formative stage. From our research it appears that stakeholders who do not have such a shared history are able to build up trust during the initial meetings in the formative stage. In this respect face-to-face contact is very important. According to Autio et al. (2008), *"[o]ften, active intervention is required from the part of the program's coordination and management function to facilitate the build-up of trust, reduce the threat of opportunism, and facilitate interaction between partners with complementary resources and needs"*. In the formative stage the prime mover can 'actively intervene' by organising and facilitating face-to-face meetings between stakeholders that allow them to assess the presence of trust. *Therefore we recommend that the prime mover facilitates face-*

84 Ledford adapted this checklist from www.nih.gov/catalyst/2002/02.05.01/page6.html 25-11-2008.

*to-face meetings between stakeholders at the beginning of the formative stage in order to build up trust*[85].

- The case studies showed that EU regulations related to nutrigenomics create protected market opportunities for (functional) food companies. 'Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods'[86] stipulates that only hard claimed functional foods will be allowed on the EU market. These hard claims can be based on the results of nutrigenomics research. *Therefore we recommend companies to invest in R&D, and to cooperate with research organisations in order to better underpin claims for functional foods.*

### 7.5.3 For policy makers

For the nutrigenomics consortia the availability of government funding showed to be a necessary pre-condition to start this new and risky type of research. Therefore in this section we focus on the role of government in the development of emerging technologies[87]:

- Funding agencies often formulate requirements that need to be met by the stakeholders before they become eligible for funding. In our case studies the development of applications was one of those requirements. This needs some critical reflection: Demanding applications in science-based emerging technologies is often at right angles to the nature of an emerging phase. In science-based emerging technologies stakeholders try in the first place to gain scientific insights. Possibilities for the application of this scientific knowledge only become perceptible afterwards. Demanding applications in this phase in a way has a counter-effect. Stakeholders that apply for funding incorporate applications in their proposals although they might be aware that it is hardly possible. This inevitably leads to negative evaluations in this respect. *Therefore we recommend governments not to imperatively require applications as an outcome of science based research.*
- Government-funded consortia like the DNC and CMS are evaluated at the close of the funding period. One of the most frequently used criteria is output measured in numbers of publications and patents. As we have seen in our research, only part of the interactive scientific knowledge outcome that resulted from the interactive learning process within the consortia consists of (codified) publications and patents. A substantial part of the scientific knowledge outcome consists of an increase in know-how, expertise and problem-solving abilities. For learning and innovation in emerging technologies this tacit outcome is of vital importance given that the build-up of know-how and expertise is essential in order to make advancements in the emerging technology. *Therefore we recommend incorporating*

85 NB These meetings should not be organised only for stakeholders that do not have a shared history, but for all stakeholders that might become involved in the consortium that is being formed.

86 See http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:EN:PDF.

87 NB The recommendations for policy makers are based on the findings in our research. We do not discuss the rationales for innovation policy in emerging technologies because this it was not the purpose of our research to make statements about these rationales. An excellent overview of rationales for innovation policy is provided by Chaminade and Edquist (forthcoming 2009).

*indicators covering tacit knowledge outcome in evaluation procedures, for example through in-depth interviews with stakeholders on the know-how and expertise they gained through the collaboration*[88].

## 7.6 Closing statement

This research has presented a Framework for Interactive Learning in Emerging Technologies. Through the exploration in case studies this framework has shown to be internally valid for the two cases studied. The concepts constitute a complete framework and the relationships were useful in describing and analysing interactive learning in the two selected nutrigenomics consortia. This research helped to take our insight into the black box of interactive learning in the development of emerging technologies one step further. Although by no means all questions have been answered and – as appears from our recommendations for further research – a great deal of research still has to be done, our research does provide stakeholders with insights that may help to facilitate the management of interactive learning in emerging technologies. Policy makers may use the results to further differentiate and focus their policies. Case studies in related fields such as pharmacogenomics and nanotechnology could help to improve the external validity of this framework.

88 The book "Evaluating Research in Context" (Spaagen, Dijstelbloem et al. 2007) provides an overview and starting point for research evaluation. The utilisation reports of Technology Foundation STW in the Netherlands can be used as a 'best practice' that already devotes attention to tacit knowledge indicators – despite the time-consuming efforts related to the retrieval of these data – in the evaluation of publicly-funded projects.

# Summary

Interactive learning has been a central concept in innovation studies since the 1980s and its influence on innovation has been shown in numerous studies since then. Interactive learning is of special importance in emerging technologies in which complementary, often tacit knowledge has to be exchanged and combined in order to learn and innovate. However, sufficient insight into the black box of the interactive learning process was lacking thus far. Therefore, the purpose of our research was to improve the insight into interactive learning of heterogeneous stakeholders in the context of emerging technologies such as nutrigenomics. In line with this we formulated the following *central research question*:

*How can interactive learning in emerging technologies be conceptualised, and how can this conceptualisation provide insights into interactive learning between heterogeneous stakeholders in nutrigenomics?*

In order to answer this question we divided our research into two parts. In Part I we developed the Framework for Interactive Learning in Emerging Technologies (FILET) and in Part II we explored the FILET in two nutrigenomics consortia.

***Interactive learning in emerging technologies***

The concept of interactive learning in innovation processes was introduced by Lundvall in 1985 (Lundvall 1985) who later defined interactive learning as *"a process in which agents communicate and even cooperate in the creation and utilisation of new economically useful knowledge"* (Lundvall, Johnson et al. 2002, p226). The positive influence of interactive learning on innovation has been acknowledged in various studies (e.g. (Von Hippel 1988; Lundvall 1992; Coombs, Green et al. 2001; Smits 2002; Moors, Enzing et al. 2003; Oudshoorn and Pinch 2003; Rohracher 2005; Smits and Hertog 2007; Boon, Moors et al. 2008; Moors, Boon et al. 2008; Smits and Boon 2008; Nahuis, Moors et al. 2009)). However, detailed insight into interactive learning itself is – still – lacking. At the same time, studies on interactive learning pre-dominantly focus on the outcome of the interactive learning process, rather than what learning is and how the outcomes are achieved (Meeus and Oerlemans 2005). This black box character of the interactive learning process asks for a framework focusing not only on the interactive learning outcome but also on the interactive learning process itself. The development of such a framework and the exploration of the developed framework in two real life cases constitutes the core of this book.

The diffusion (Rogers 1962) or technological performance (Foster 1986) of innovations can be depicted by an S-curve with various life stages (Tidd, Bessant et al. 2001). Technologies go through several life stages from invention (the original idea) to

innovation (the successful economic and/or social application of the invention in a product, process or service). *"Emergence is the process or event of something coming into existence. For technological development this notion then relates to the very early stages of technological development."* (Van Merkerk and Van Lente 2005).

Knowledge is often still tacit in an emerging technology because not all new knowledge has been codified in e.g. scientific articles (Senker 1995; Arundel and Geuna 2004). Even when knowledge has been codified, it sometimes needs tacit explanation, for instance on how to perform experiments (Senker 1995; Howells 2002). Interactive learning facilitates the interchange and combination of complementary knowledge in codified and tacit form (Malmberg and Maskell 1999; Doloreux 2004). For stakeholders, interaction and collaboration is important because it is difficult for individual stakeholders to keep up with the rapid developments (Ponds 2008), especially in emerging technologies like nutrigenomics where complementary knowledge from nutrition and genomics has to be combined. The growth in scientific (sub)fields (Stichweh 1996) and interdisciplinary fields like nutrigenomics (Ponds 2008) has resulted in a division of highly specialised knowledge among heterogeneous stakeholders. The specialisation into (sub)fields has also resulted in more and more highly specialised instruments and research methods and has led to a further specialisation in know-how and expertise regarding these instruments and methods (Katz and Martin 1997). Related to the increase in specialisation are the increased costs for research. The need to combine complementary, specialised and often tacit knowledge and research methods, and the search for human resources and research funding, require collaboration of and interactive learning between stakeholders.

Interaction between stakeholders in an emerging technology is not only important for the advancement of science. In the emerging phase, the technology is still 'fluid' and it is difficult for stakeholders to specify desired characteristics. When the technology becomes more 'solidified' due to increasing vested interests, stakeholders know far better what they want, but the options to intervene decrease. This trade-off is known as the Collingridge dilemma (Collingridge 1980). Therefore, interactive learning between stakeholders is also important in the early phase of technology development for the co-construction and realisation of a shared vision among the stakeholders. Whereas knowledge is necessary to bring forth new product, process or service innovations, a shared vision can act as a driver and shared frame of reference for the further development of the technology (Checkland 1988; Vergragt 1988; Smits 2005). In a later phase of development this shared vision also will contribute to the quality and acceptance of innovations based on the technology.

To conclude, interactive learning is important in emerging technologies. Interactive learning facilitates the combination of resources and complementary (tacit) knowledge from heterogeneous stakeholders, the development of a shared vision and stimulates the advancement of science and, eventually, the development of innovations.

### *Framework for Interactive Learning in Emerging Technologies (FILET)*

In Part I of our research we constructed the Framework for Interactive Learning in Emerging Technologies. The FILET is a heuristic that can help us to understand interactive learning in emerging technologies. Interactive learning is a process with an outcome and the process itself is influenced by conditions.

The outcome of interactive learning can be divided into an *interactive scientific knowledge outcome* and the *realisation of a shared vision*. The realised shared vision is the result of the co-construction of a shared vision by the stakeholders at the beginning of the collaboration and the extent to which the interacting stakeholders are able to realise that shared vision.

The interactive learning outcome is influenced by the main elements of the interactive learning process. These elements include the *prime mover, network formation, intermediary,* and the *knowledge flows* between the stakeholders. The prime mover takes the initiative to bring complementary stakeholders together[89]. During the network formation the stakeholders start to form a consortium. The knowledge flows contain the knowledge that is produced and exchanged between the stakeholders. Intermediaries can help in translating knowledge and bridging possible knowledge gaps between the individual stakeholders.

The elements of the interactive learning process in turn are influenced by a set of proximity conditions, in particular the *geographical, cognitive, regulatory, cultural, social*, and the *organisational proximity*. Geographical proximity refers to the physical distance between stakeholders and cognitive proximity to the distance between their technological foci. Regulatory proximity refers to (inter)national regulations, government funding schemes and mutual agreements that can influence the interactive learning process. Cultural proximity refers to the informal rules adhered to by the stakeholders. Social proximity indicates the presence of trust between stakeholders and organisational proximity points at the flexibility and coordination of research within the consortium.

***Nutrigenomics, an emerging technology***

The development of nutrigenomics has caused great expectations about future applications for personal health care. Nutrigenomics is the study of the interaction between nutrition and the genome, and envisioned applications encompass nutrigenomics health tests, dietary services and so-called functional foods with an additional health promoting benefit (Ronteltap, van Trijp et al. 2007). These applications could for example be used in the prevention and treatment of genetically predisposed nutrition-related diseases like the Metabolic Syndrome. The Metabolic Syndrome is a combination of risk factors that eventually lead to cardio-vascular disease (Kahn, Buse et al. 2005). The Metabolic Syndrome starts with obesity. Obesity is responsible for 10-13% of deaths and 2-8% of health care costs in Europe, and is, therefore, *"one of the greatest public health challenges of the 21st century"* (www.who.int/nutrition/topics/obesity/en/index.html 17-11-2008).

Nutrigenomics looks promising for consumers, patients and the health care systems as a whole. Researchers however are still in the early phase of this innovation trajectory. At the moment they are focusing on the unravelling of the interaction between nutrition and the genome. For this research complementary knowledge from stakeholders with backgrounds in nutrition research, genetics research and the food industry has to be combined. Heterogeneous stakeholders have to interact in order to learn and innovate on the boundaries of these complementary knowledge pools. Therefore *interactive learning* is crucial for innovation in nutrigenomics.

89 For an elaborate explanation of the concepts within the FILET see Chapter 2.

Nutrigenomics is an emerging technology because it has three characteristics typical of an emerging technology:

- There is no dominant design or definition of the technology. For our research we defined nutrigenomics as: research into the relationship between genomes, nutrition and disease (risk) and the future applications that might result from that research.
- While there are no commercially applications derived from the emerging technology as yet, there are high expectations for future applications. Expected applications (innovations) resulting from nutrigenomics research are functional foods, nutrigenomics research as a service innovation to substantiate hard claims for functional foods based on scientific evidence, and nutrigenomics tests and dietary advice. These applications could lead to opportunities for preventing and treating nutrition-related, genetically predisposed diseases like the Metabolic Syndrome.
- There is a perceptible increase in linkages between stakeholders in emerging technologies. For nutrigenomics, complementary stakeholders have initiated the formation of consortia in which they collaborate in nutrigenomics research.

Analysis of patents and publications showed that nutrigenomics is an emerging technology that attracts a great deal more attention than other technologies, as may be concluded from relative growth in number of patents (i.e. a so-called hot-spot analysis). The presence of co-publications and co-patents indicates collaboration and interactive learning within the emerging technology of nutrigenomics.

Interactive learning in emerging technologies is a phenomenon that occurs in real life. The phenomenon is socially embedded and it is not possible to take it out of this context (as one would do in a lab experiment in a controlled environment). In these real-life phenomena the boundaries between the phenomenon and the surrounding social context are often not clear, and exogenous mechanisms might also be of importance. Case studies emphasise the rich real life of phenomena and their surrounding context. Given this real life character and the fuzzy boundaries between interactive learning and its social context, the case study becomes the preferred research strategy for the exploration of interactive learning in emerging technologies.

We performed an exploration of the FILET in two nutrigenomics consortia selected from a list of eight consortia using specific selection criteria (i.e. similarity, interactive learning outcome, nutrigenomics as the core business, and availability and accessibility of empirical data): The Dutch Nutrigenomics Consortium (DNC) and the German Competence Network Metabolic Syndrome (CSM).

#### *Exploration of the FILET in Nutrigenomics consortia*

In Part II of our research we explored the FILET in the Dutch Nutrigenomics Consortium (DNC) and the German Competence Network Metabolic Syndrome (CSM). The *interactive scientific knowledge outcome* of the consortia included (co-) publications and standards (all codified), and an increase in tacit knowledge in the form of know-how, expertise and problem-solving capabilities.

The *shared visions* that were co-constructed at the beginning of the consortia were only partly realised. Through the scientific research conducted within the consortium

and the resulting *interactive scientific knowledge outcome* it became evident that more nutrigenomics research is needed to fully understand the intricate relationship between the genome and nutrition. Consequently the stakeholders could only realise the first objective of the shared visions (interactive, scientific knowledge) but failed to realise the second objective: useful applications.[90]

The main elements of the interactive learning process are the *prime mover, network formation, knowledge flows* and *intermediary.* In the case studies we observed a typical 'sequence of events' in the interactive learning process. First, initiated by the prime mover, a network of complementary stakeholders is formed. During the network formation a shared vision is co-constructed. Second, during research conducted within the consortia knowledge flows between the stakeholders results in interactive learning and increased scientific insight. The exchange of knowledge is sometimes facilitated by an intermediary. The scientific insights determined the extent to which the stakeholders could realise the shared vision.

The prime movers initiated the formation of networks driven by a sense of urgency to realise promising applications and the perceived need to bring together knowledge and resources from a heterogeneous set of stakeholders. During the network formation the stakeholders co-constructed a shared vision. In the DNC case the individual visions were integrated into a shared vision with the help of an intermediary by designing interrelated work packages. Individual work packages corresponded with the expertise of the leading stakeholders, and the work packages were subsequently integrated in the 'integrating' work package. The formation of a network of stakeholders from nutrition and genomics fields was necessary to gain further scientific insight into nutrigenomics. In the CMS case the shared vision only was an umbrella that encompassed the stakeholders' individual visions.

The knowledge flows between the stakeholders resulted in an increase in interactive scientific knowledge outcome as manifested in scientific articles, and tacit know-how and expertise. During the research within the DNC, mouse models and TNO fulfilled an important role as the intermediary in this interactive learning process by functioning as a shared frame of reference, and the facilitation of exemplification projects, respectively. Ultimately however, the stakeholders were only able to realise the first objective of the shared vision. During the lifetime of the consortia it became clear that it was still too early to transform these scientific results into practical applications. To do this, more scientific questions regarding the complex relation between the genome, nutrition and disease have to be answered.

*Geographical proximity* and *cognitive distance* had a positive influence on the prime mover, network formation and the knowledge flows. *Regulatory proximity at the macro level* (funding, EU regulations) positively influenced the prime mover and the network formation, and *regulatory proximity at the meso level* had a positive influence on the knowledge flows. *Organisational* and *social proximity* had a positive effect on the knowledge flows. For *cultural proximity* we have to conclude that, despite the cultural differences between research institutes and firms, the stakeholders did have a similar focus on publications and patents.

90 The interactive learning outcome of the consortia is summarised in Table 13.

*Geographical, cognitive, cultural* and *regulatory proximity at the macro* level were already determined before collaboration in the consortia started. Regulatory *proximity at the meso level* and *organisational proximity* were shaped during the first phases of the formation process. Trust (i.e. *social proximity*) was already present between stakeholders that had a shared history. However, we observed that the stakeholders with no shared history assessed the presence of trust during network formation by organising face-to-face meetings within the context of the consortium.

The major conclusions resulting from the exploration of the FILET in the nutrigenomics case studies are:

- Government funding was a *necessary pre-condition* for the nutrigenomics consortia. Without the availability of government funding the stakeholders would not have embarked on the long term, risky and expensive nutrigenomics research.
- The case studies showed a 'sequence of events' in interactive learning. First, a *formative stage* in which the prime mover contacts complementary stakeholders and the network is formed. In the formative stage a shared vision is co-constructed by the stakeholders. Second, a *research stage* in which the scientific research is performed. Knowledge between the stakeholders is exchanged and combined in the research stage. This interactive learning results in an interactive scientific knowledge outcome as expressed in the scientific articles and in an increase of tacit knowledge. On the basis of these scientific insights the stakeholders can determine to what extent it is realistic to realise the shared vision they co-constructed at the beginning of the collaboration.
- Some dimensions of proximity that influence the interactive learning process are not fully determined at the beginning of the collaboration and are further defined during the formative stage:
  - *Social proximity* between stakeholders is present if they have a shared history. In the case studies not all stakeholders had a shared history and those stakeholders used the first meetings during the formative stage of the consortium to assess whether there was trust between them.
  - *Regulatory proximity* at the meso level is indicated by mutual agreements settling IPR and NDA issues. These mutual agreements are drafted and signed during the formative stage before the actual research collaboration between the stakeholders begins.
  - During the formative stage *the stakeholders* agree upon how their research will be organised within the consortium. This arrangement determines the *organisational proximity*.
- In the *research stage* we observed that objects like mouse models also fulfilled an intermediary function. These objects acted as a common point of reference that helped the heterogeneous stakeholders to cross the boundaries between their knowledge fields (i.e. nutrition and genetics). Thus, the intermediary function can be fulfilled not only by a stakeholder, but also by 'boundary objects'.

These major conclusions are incorporated in an adapted visual representation of the FILET (Figure 39).

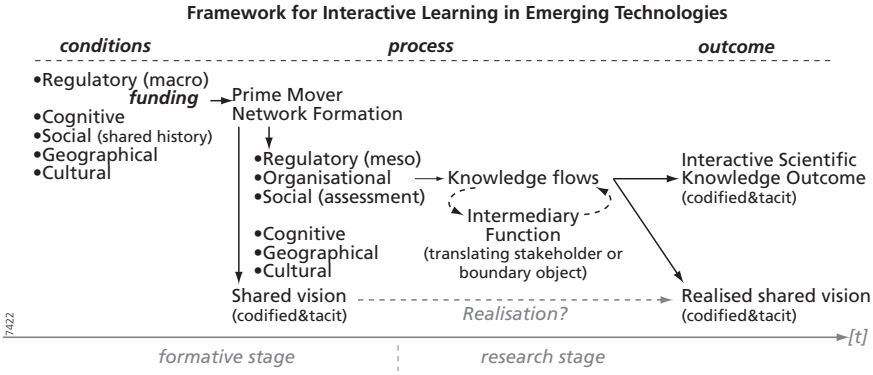



**Figure 39** FILET based on major conclusions of case studies

### *Conclusion and recommendations*

In this research a Framework for Interactive Learning in Emerging Technologies was developed. Through the exploration in case studies this framework has shown to be internally valid for the two cases studied. The concepts constitute a complete framework and the relationships were useful in describing and analysing interactive learning in the two selected nutrigenomics consortia. This research helped to take our insight into the black box of interactive learning in the development of emerging technologies one step further. Policy makers may use the results to further differentiate and focus their policies: i.e. not to imperatively require applications as an outcome of science based research, and to incorporate indicators covering tacit knowledge outcome in evaluations. For consortia stakeholders we recommend to use a checklist for the so-important consortium agreement and to build-up trust at the beginning of the formative stage. For companies we recommend to invest in R&D in order to substantiate claims for functional foods.

# Samenvatting

Interactief leren is al sinds de jaren 80 een centraal concept binnen de innovatie studies en de invloed van interactief leren op innovatie(succes) is in talrijke onderzoeken aangetoond. Interactief leren is voornamelijk van belang in emergente technologieën waarin complementaire, vaak tacit[91] kennis uitgewisseld en gecombineerd moet worden om te innoveren. Inzicht in de black box van het interactief leerproces ontbrak totnogtoe. Daarom was het doel van dit onderzoek het verkrijgen van inzicht in en het verbeteren van het interactief leerproces tussen heterogene stakeholders in emergente technologieën, zoals nutrigenomics. Hiervoor werd de volgende centrale onderzoeksvraag geformuleerd:

*Hoe kan interactief leren in emergente technologieën worden geconceptualiseerd, en hoe kan deze conceptualisering inzicht verschaffen in interactief leren tussen heterogene stakeholders in nutrigenomics?*

Om een antwoord op deze vraag te geven bestond het onderzoek uit twee delen. In het eerste deel is het Framework for Interactive Learning in Emerging Technologies (FILET) ontwikkeld. Vervolgens is dit framework in het tweede gedeelte geëxploreerd in twee nutrigenomics consortia.

***Interactief leren in emergente technologieën***

Lundvall introduceerde het concept interactief leren in 1985 (Lundvall 1985) en hij definieerde interactief leren als *"a process in which agents communicate and even cooperate in the creation and utilisation of new economically useful knowledge"* (Lundvall, Johnson et al. 2002, p226). De positieve invloed van interactief leren op innovatie is aangetoond in verschillende studies (e.g. (Von Hippel 1988; Lundvall 1992; Coombs, Green et al. 2001; Smits 2002; Moors, Enzing et al. 2003; Oudshoorn and Pinch 2003; Rohracher 2005; Smits and Hertog 2007; Boon, Moors et al. 2008; Moors, Boon et al. 2008; Smits and Boon 2008; Nahuis, Moors et al. 2009)). Echter, gedetailleerd inzicht in interactief leren ontbreekt nog (steeds). Tegelijkertijd is het meeste interactief leeronderzoek gericht op de leeruitkomst en niet zozeer op het interactieve leerproces zelf en hoe dit tot leeruitkomsten leidt (Meeus and Oerlemans 2005). Daarom is het van belang een framework te ontwikkelen dat niet alleen naar de interactieve leeruitkomst kijkt, maar ook naar het interactieve leerproces. De kern van dit onderzoek is de ontwikkeling van een dergelijk framework en de exploratie hiervan in cases van een emergente technologie.

91 'Tacit' kennis is kennis die (nog) niet 'gecodicifeerd' is in bijvoorbeeld wetenschappelijke artikelen.

De diffusie (Rogers 1962) of technische performance (Foster 1986) van innovaties kan worden weergegeven in een S-curve die bestaat uit verschillende fasen (Tidd, Bessant et al. 2001). Technologieën doorlopen deze fasen van inventie (het originele idee) tot innovatie (de maatschappelijke en/of economische inbedding van een idee in een product, proces of dienst). *"Emergence is the process or event of something coming into existence. For technological development this notion then relates to the very early stages of technological development."* (Van Merkerk and Van Lente 2005).

Kennis is in emergente technologieën vaak tacit omdat nog niet alle kennis gecodificeerd is, bijvoorbeeld in wetenschappelijke artikelen (Senker 1995; Arundel and Geuna 2004). Maar ook wanneer kennis al gecodificeerd is, is een tacit uitleg vaak noodzakelijk om bijvoorbeeld te weten hoe een bepaald experiment uitgevoerd moet worden (Senker 1995; Howells 2002). Interactief leren faciliteert de uitwisseling en combinatie van complementaire kennis in zowel gecodificeerde als tacit vorm (Malmberg and Maskell 1999; Doloreux 2004).

Voor stakeholders is interactie en samenwerking belangrijk omdat het voor individuele stakeholders moeilijk is om snelle ontwikkelingen bij te houden (Ponds 2008), met name in emergente technologieën zoals nutrigenomics waarbij complementaire kennis van verschillende vakgebieden gecombineerd moet worden (i.c. genomics en voeding). De toename van wetenschappelijke (sub)velden (Stichweh 1996) en interdisciplinaire velden zoals nutrigenomics (Ponds 2008) heeft geleid tot een verdeling van hoog gespecialiseerde kennis tussen heterogene stakeholders. Dit heeft tegelijkertijd geleid tot gespecialiseerde instrumenten en onderzoeksmethoden, hetgeen op haar beurt weer heeft geleid tot een verdere specialisatie van know-how en expertise aangaande deze instrumenten en methoden (Katz and Martin 1997), wat weer heeft geleid tot een toename van de kosten voor onderzoek. Daarom is samenwerking en interactief leren tussen heterogene stakeholders noodzakelijk voor het combineren van complementaire, specialistische, vaak tacit kennis en onderzoeksmethoden, en het aanboren van human resources en onderzoeksbudget.

Interactief leren tussen stakeholders in emergente technologieën is niet alleen van belang voor wetenschappelijke vooruitgang. In de emergente fase is technologie nog fluïde en is het voor stakeholders nog moeilijk om wensen aangaande de technologie vast te leggen. In een later stadium zijn de (gebruikers)wensen duidelijker, maar is de technologie solide en moeilijker te (her)vormen. Dit dilemma staat bekent als het Collingridge dilemma (Collingridge 1980). Daarom is interactief leren tussen stakeholders gedurende de emergente fase ook van belang voor de co-constructie van een gemeenschappelijke visie en de realisatie hiervan. Waar (wetenschappelijke) kennis belangrijk is voor de ontwikkeling van nieuwe producten, processen en diensten, kan een gedeelde visie fungeren als een stimulans en gemeenschappelijk vertrekpunt voor verdere technologische ontwikkeling (Checkland 1988; Vergragt 1988; Smits 2005). In een latere fase kan de gemeenschappelijke visie ook bijdragen aan de kwaliteit en acceptatie van innovaties die gebaseerd zijn op de technologie.

Concluderend: Interactief leren is belangrijk in emergente technologieën omdat het de combinatie van resources (human capital en onderzoeksfinanciering),

complementaire (tacit) kennis van heterogene stakeholders, de ontwikkeling van een gemeenschappelijke visie, wetenschappelijke ontwikkelingen en innovaties stimuleert.

***Framework for Interactive Learning in Emerging Technologies (FILET)***

In het eerste deel van het onderzoek is het Framework for Interactive Learning in Emerging Technologies geconstrueerd. Het FILET is een heuristiek die helpt met het verkrijgen van inzicht in interactief leren in emergente technologieën. Interactief leren is een proces met een uitkomst en het proces wordt beïnvloedt door condities.

De interactieve leeruitkomst kan onderverdeeld worden in *interactive scientific knowledge outcome* (i.e. wetenschappelijke kennis) en de *realisation of a shared vision* (i.e. een gemeenschappelijke visie)[92]. De realisation of a shared vision is het resultaat van de co-constructie van de shared vision door de stakeholders aan het begin van de samenwerking en de mate waarin deze visie door de stakeholders werd gerealiseerd gedurende de samenwerking[93].

De interactieve leeruitkomst wordt beïnvloed door het interactieve leerproces. De elementen van het interactief leerproces zijn de *prime mover, network formation, intermediary,* en de *knowledge flows* tussen de stakeholders. De prime mover neemt het initiatief om complementaire stakeholders samen te brengen. Gedurende de network formation vormen de stakeholders een consortium. De knowledge flows bevatten de kennis die geproduceerd wordt door en uitgewisseld tussen de stakeholders. Intermediaries kunnen kennis vertalen en mogelijke kennislacunes tussen stakeholders helpen te overbruggen.

De elementen van het interactief leerproces worden op hun beurt beïnvloed door een set van proximity condities: *geographical, cognitive, regulatory, cultural, social,* en *organisational proximity*. Met geographical proximity wordt de fysieke afstand tussen stakeholders bedoeld en met cognitive proximity de afstand tussen hun technologische focus. Regulatory proximity heeft betrekking op (inter)nationale wet- en regelgeving, overheidsfinanciering voor onderzoek en afspraken (contracten) tussen stakeholders die het interactief leerproces beïnvloeden. Informele regels waaraan stakeholders zijn gebonden vallen onder cultural proximity. Social proximity geeft de aanwezigheid van vertrouwen tussen de stakeholders aan en organisational proximity omvat de flexibiliteit en coördinatie van het onderzoek binnen het consortium.

***Nutrigenomics, een emergente technologie***

Met nutrigenomics wordt onderzoek aangeduid naar de interacties tussen voeding (nutri) en genomics. De ontwikkelingen binnen nutrigenomics hebben geleid tot grote verwachtingen aangaande toekomstige toepassingen voor personal health care. De mogelijke toekomstige toepassingen omvatten nutrigenomics gezondheidstest, dieetadvies en zogenaamde functional foods die een gezondheidsbevorderend effect hebben (Ronteltap, van Trijp et al. 2007). Deze toepassingen kunnen bijvoorbeeld gebruikt worden voor de preventie en behandeling van genetisch bepaalde

92 In deze samenvatting worden de Engelse termen van de concepten gebruikt zoals deze door het gehele boek gebruikt worden.

93 Zie hoofdstuk 2 voor een gedetailleerde beschrijving van de concepten die deel uitmaken van het FILET.

voedingsgerelateerde ziektes zoals het Metabole Syndrome. Het Metabole Syndrome is een combinatie van risicofactoren die uiteindelijk kunnen leiden tot hart- en vaatziekten (Kahn, Buse et al. 2005). Het begin van het Metabole Syndrome wordt gekenmerkt door obesitas, hetgeen in Europe verantwoordelijk is voor 10-13% van de sterfgevallen en 2-8% van de ziektekosten. Daarom is obesitas *"one of the greatest public health challenges of the 21st century"* (www.who.int/nutrition/topics/obesity/en/index.html 17-11-2008).

Nutrigenomics lijkt veelbelovend voor consumenten, patiënten en het gezondheidszorgstelsel in haar geheel. Momenteel verkeert nutrigenomics echter in de emergente fase van ontwikkeling en onderzoekers zijn voornamelijk bezig met het ontrafelen van de interactie tussen voedsel en genen. Voor dit onderzoek is het combineren van complementaire kennis van stakeholders uit het voedingsonderzoek, de genetica en de voedselindustrie noodzakelijk. Deze stakeholders moeten met elkaar interacteren om te leren en innoveren over de grenzen tussen deze complementaire kennisvelden heen. Daarom is interactief leren van belang voor het nutrigenomics innovatieproces.

Nutrigenomics voldoet aan de drie typische eigenschappen van een emergente technologie:

- Er is geen 'dominant design' of definitie. Voor ons onderzoek hebben we nutrigenomics gedefinieerd als: onderzoek naar de relatie tussen genoom, voeding en (de kans op) ziekte en de toekomstige toepassingen die uit dit onderzoek kunnen voortkomen.
- Vooralsnog zijn er nog geen commercieel verkrijgbare nutrigenomics producten, maar er zijn wel hooggespannen verwachtingen omtrent toekomstige toepassingen. Verwachte toepassingen zijn de eerder genoemde functional foods, nutrigenomics onderzoek als service innovatie die het mogelijk maakt harde claims voor functional foods wetenschappelijk te onderbouwen en nutrigenomics tests en dieetadvies.
- Er is een zichtbare toename van het aantal relaties en interacties tussen nutrigenomics stakeholders. In nutrigenomics hebben complementaire stakeholders consortia gevormd waarin ze samenwerken in nutrigenomics onderzoek.

Patent en publicatie analyse heeft laten zien dat nutrigenomics een emergente technologie is die meer aandacht krijgt dan andere technologieën, zoals bijvoorbeeld zichtbaar in de relatieve groei in patenten (een zogenaamde hot-spot analyse). De aanwezigheid van co-publicaties en co-patenten duidt op samenwerking en interactief leveren in nutrigenomics.

Interactief leren in emergente technologieën is een fenomeen dat in 'real life' plaatsvindt. Het fenomeen is sociaal ingebed en het is daarom ook niet mogelijke om het uit deze sociale context te extraheren (zoals bijvoorbeeld in een experiment). Bij real life fenomenen zijn de grenzen tussen het fenomeen en de omliggende context niet altijd even duidelijk en kunnen ook exogene factoren van invloed zijn. Case studies benadrukken de rijkheid van een real life fenomeen en de omliggende context. Gegeven het real life karakter van interactief leren, heeft de case study de voorkeur

als onderzoeksmethode voor de exploratie van het FILET in emergente technologieën. Uit acht kandidaat-cases zijn twee nutrigenomics consortia geselecteerd m.b.v. selectiecriteria: het Dutch Nutrigenomics Consortium (DNC) en het German Competence Network Metabolic Syndrome (CSM)

***Exploratie van het FILET in nutrigenomics consortia***

In het tweede deel van ons onderzoek hebben we het FILET geëxploreerd in het Dutch Nutrigenomics Consortium (DNC) en het German Competence Network Metabolic Syndrome (CSM). De *interactive scientific knowledge outcome* van deze consortia omvatte (co-) publicaties en standaarden (gecodificeerd), en een toename in tacit kennis in de vorm van know-how, expertise en probleemoplossende vermogen.

De *shared visions* die aan het begin werden geco-construeerd waren aan het einde gedeeltelijk gerealiseerd. Door het wetenschappelijk onderzoek uitgevoerd binnen het consortium en de resulterende *interactive scientific knowledge outcome* werd duidelijk dat meer nutrigenomics onderzoek nodig is om de ingewikkelde relatie tussen genen en voedsel volledig te begrijpen.

Hierdoor konden de stakeholders alleen het eerste doel van hun gemeenschappelijke visie verwezenlijken (i.e. verkrijgen van wetenschappelijke kennis) maar niet het tweede doel: bruikbare applicaties.[94]

De elementen van het interactieve leerproces zijn de *prime mover, network formation, knowledge flows* en *intermediary*. In de case studies werd een duidelijke volgorde van events zichtbaar in het interactief leerproces. Eerst werd, geïnitieerd door de prime mover, een netwerk van complementaire stakeholders gevormd. Gedurende de network formation werd een shared vision geco-construeerd. Hierna werd het onderzoek in het consortium uitgevoerd waarbij de knowledge flows tussen de stakeholders leidden tot interactief leren en een toename van wetenschappelijke inzichten. De uitwisseling van kennis werd hierbij soms gefaciliteerd door een intermediary. De verkregen wetenschappelijke inzichten bepaalden de mate waarin de stakeholders de shared vision konden realiseren.

Bij het initiëren van de network formation werden de prime movers gedreven door een 'sense of urgency' voor het realiseren van veelbelovende applicaties en de noodzaak om complementaire kennis en resources van heterogene stakeholders samen te brengen. Gedurende de network formation werd de shared vision door de stakeholders geco-construeerd. In het DNC werden de individuele visies van de stakeholders met behulp van een intermediary geïntegreerd in een shared vision door gebruik te maken van 'interrelated work packages'. De individuele work packages kwamen overeen met de expertise van de leidende stakeholders in het work package; uiteindelijk werden alle work packages geïntegreerd in een 'integrating' work package. De network formation van stakeholders met expertise in voeding en genomics was noodzakelijk voor het vergaren van wetenschappelijk inzicht in nutrigenomics. In de CMS case fungeerde de shared vision als een paraplu die de individuele visies van de stakeholders omvatte.

De knowledge flows tussen de stakeholers leidden tot een toename van interactive scientific knowledge outcome die zichtbaar was in wetenschappelijke artikelen,

94 De interactive learning outcome van de consortia is samengevat in Table 13.

tacit know-how en expertise. De gebruikte muismodellen en TNO fungeerden als intermediaries in het interactief leerproces in het DNC omdat ze respectievelijk fungeerden als een 'shared frame of reference' en zogenaamde 'exemplification projects' mogelijke maakten. Uiteindelijk waren de stakeholders in staat alleen het eerste doel van hun shared vision te verwezenlijken. Gedurende het bestaan van de consortia werd het duidelijk dat het nog te vroeg was om wetenschappelijke inzichten te vertalen in praktische applicaties. Om dat te bereiken moeten nog meer wetenschappelijke vragen aangaande de relatie tussen voeding, genen en ziektes beantwoord worden.

*Geographical proximity* en *cognitive distance* hadden een positieve invloed op de prime mover, network formation en de knowledge flows. *Regulatory proximity at the macro level* (financiering, EU wet- en regelgeving) beïnvloedden de prime mover en network formation op een positieve wijze, en *regulatory proximity at the meso level* had een positief effect op de knowledge flows. *Organisational* en *social proximity* hadden een positieve invloed op de knowledge flows. Ondanks de culturele verschillen tussen onderzoeksinstituten en bedrijven, moeten we voor *cultural proximity* concluderen dat de stakeholders een gelijke focus hadden op patenten en publicaties.

*Geographical, cognitive, cultural* en *regulatory proximity at the macro level* waren reeds voor de samenwerking in de consortia gedefinieerd. *Regulatory proximity at the meso level* en *organisational proximity* kregen pas gestalte gedurende de eerste fase van de formatie. Tussen de stakeholders die elkaar al kenden uit eerdere samenwerkingsverbanden was vertrouwen (i.e. *social proximity*) reeds aanwezig; de stakeholders die elkaar niet kenden gebruikten de eerste face-to-face bijeenkomsten om na te gaan of zij dachten elkaar gedurende de samenwerking binnen de context van het consortium te kunnen vertrouwen.

De voornaamste conclusies die uit de exploratie van het FILET in de nutrigenomics case studies getrokken kunnen worden zijn:

- Overheidsfinanciering was een *necessary pre-condition* voor de vorming van de nutrigenomics consortia. De stakeholders zouden niet aan het risicovolle, dure, lange termijn nutrigenomicsonderzoek begonnen zijn wanneer er geen overheidsfinanciering beschikbaar zou zijn geweest.
- De case studies lieten een 'sequence of events' in het interactieve leerproces zien. Eerst is er een *formative stage* waarin de prime mover contact opneemt met complementaire stakeholders en de network formation plaatsvindt. In de formative stage wordt een shared vision geco-constructed door de stakeholders. Hierna is er een *research stage* waarin het wetenschappelijk onderzoek wordt uitgevoerd. In de research stage wordt kennis uitgewisseld tussen en gecombineerd door de stakeholders. Dit interactieve leren resulteert in interactive scientific knowledge outcome zoals zichtbaar in wetenschappelijke artikelen en een toename in tacit kennis. Op basis van deze verkregen kennis kunnen de stakeholders nagaan in hoeverre de realisatie van de shared vision realistisch is.
- Sommige proximity condities die het interactief leerproces beïnvloeden zijn nog niet volledige bepaald aan het begin van de samenwerking en worden verder gevormd gedurende de formative stage:
  - *Social proximity* bestaat tussen stakeholders die al een gedeeld verleden hebben ('shared history'). Nog niet alle stakeholders in de case studies hadden een

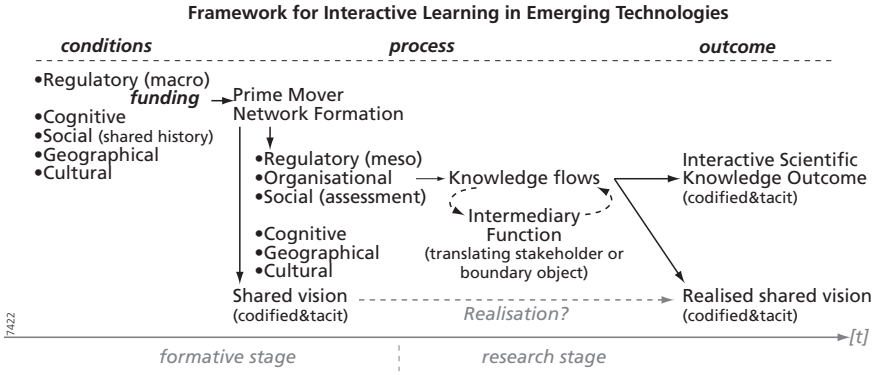



**Figure 40** FILET gebaseerd op case study conclusies

gemeenschappelijk verleden en daarom gebruikten zij de eerste bijeenkomsten in de formative stage om na te gaan of zij het idee hadden elkaar te kunnen vertouwen.

- *Regulatory proximity at the meso level* wordt bepaald door contracten aangaande IPR en NDA. Deze contracten worden opgesteld gedurende de formative stage, voordat de onderzoekssamenwerking tussen de stakeholders begint.
- In de formative stage maken de stakeholders afspraken over de organisatie van het onderzoek. Dit bepaalt de *organisational proximity*.

- We zagen dat in de *research stage* ook objecten zoals muismodellen de rol van intermediary kunnen vervullen. Deze objecten fungeren als een 'common point of reference' waardoor de heterogene stakeholders de grenzen tussen hun kennisvelden (i.e. voeding en genetics) konden overbruggen. Zodoende hoeft de intermediary function niet alleen vervult te worden door een stakeholder, maar kan dit ook gebeuren door 'boundary objects'.

De bovenstaande conclusies zijn verwerkt in een aangepaste visuele weergave van het FILET (Figure 40).

***Conclusie en aanbevelingen***

In dit onderzoek is een Framework for Interactive Learning in Emerging Technologies (FILET) ontwikkeld. De exploratie van het FILET toonde aan dat het framework intern valide is voor de twee cases. De concepten vormen een compleet framework en de relaties tussen de concepten waren bruikbaar voor het beschrijven en analyseren van interactief leren in de cases. Zodoende heeft het onderzoek bijgedragen aan het verder openen van de black box van interactief leren in emergente technologieën. Beleidsmakers kunnen de resultaten gebruiken voor een verdere differentiatie en focus van hun beleid: bijvoorbeeld door niet automatisch applicaties als uitkomst van fundamenteel onderzoek te vereisen en indicatoren in evaluaties op te nemen die ook rekening houden met tacit kennis. Stakeholders in consortia zouden een checklist (zie hoofdstuk 7) kunnen gebruiken voor het opstellen van het contract ('mutual agreement') en het opbouwen van vertrouwen ('trust') aan het begin van de formative stage. Deze twee elementen zijn uitermate belangrijk voor het interactief leerproces

en innovatie. Gelet op EU-wetgeving is het voor bedrijven verstandig in R&D te investeren om zodoende harde claims voor functional foods wetenschappelijk te onderbouwen.

# Annex I IPC classes and publications search strategies

**Table 14** Used IPC classes

| | |
|---|---|
| Nutrition | A01G, A01H, A01J, A23C, A23D, A23F, A23J, A23L, A23P, C07G NOT C07G-011 |
| Genomics | A61K-031, A61K-033, A61K-035, A61K-038, A61K-039, A61K-041, A61K-047, A61K049-00, A61K-048, C12N-015, C07H-021/02, C07H-021/04, C07G, C07K-004, C07K-014, C07K-016, C07K-017, C07K-019, C12F-003/04, C12F-003/08, C12F-003/10, C12F-005, C12N-001, C12N-003, C12N-007, C12N-009, C12N-011, C12N-013, C12P NOT C12P-033, C12S, C13K |

**Table 15** Related IPC food classes

| Group | Nutrition IPC | Description |
|---|---|---|
| Plant products | A01G | horticulture; cultivations of vegetables, flowers, rice, fruit, vines, hops, or seaweed; forestry; watering |
| | A01H | new plants or processes for obtaining them; plant reproduction by tissue culture techniques |
| Dairy | A01J | manufacturing of dairy products |
| | A23C | dairy products, e.g. milk, butter, cheese; milk or cheese substitutes; making thereof |
| Fats | A23D | edible oils or fats, e.g. margarines, shorteings, cooking oils |
| Coffee/tea | A23F | coffee; tea; their substitutes; manufacture, preparation, or infusion thereof |
| Others | A23J | protein composetions for foodstuffs; wirking-up proteins for foodstufs; phosphatide compositions for foodstuffs |
| | A23L | foods, foodstuffs, or non-alcoholic beverages, not covered by subclasses A23B to J; their preparation or treatment, e.g. cooking, modification of nutritive qualities, physical treatment; preservation of foods or foodstuffs, in general |
| | A23P | shaping or working of foodstuffs, not fully covered by a single other subclass |
| | C07G NOT C07G-011 | compounds of unknown constitution |

**Table 16** Publication search strategies – the two search strategies for defining the two genomics fields. For every strategy the keywords used and the number of publications found are displayed.

| Genomics field | Strategy 1 | Strategy 2 | Combination |
|---|---|---|---|
| Nutrigenomics | 'nutrigenomic(s)', 'nutrigenetic(s)' – 108 | Genetics ('genetic(s), genomic(s)') AND Nutrition ('nutrition, nutritional, nutricial, nutraceutical, nutriceutical, nutrient, food factor, dietary compound, functional food, supplement pill, dietary intervention') AND Disease ('cancer, obesity, obisitas, cardio vascular disease, cardiovascular disease, non insulin dependent diabetes, type 2 diabetes, adult onset diabetes, osteoporosis, metabolic syndrome') – 1517 | Strategy 1 OR strategy 2 – 1579 |

# Annex II Overview of the interviewees

| Interviewee | Organisation | Function |
|---|---|---|
| **Explorative interviews** | | |
| Vincent Buskens | UU ICS | associate professor department of sociology |
| Stanley Brul | Unilever/UvA | professor molecular biology & microbial food safety |
| Theo Verrips | UU/Unilever | professor cell bioloty |
| Jeroen Hugenholtz | NIZO | principal scientist food fermentation |
| Ysbrand Poortman | VSOP | founder/chair |
| Lucien Hansen | DEINING | consultant |
| Frans van Dam | CSG | communication officer |
| Minke In 't Velt | | general practitioner |
| **'scientometrics' interviews** | | |
| Ulrich Schmoch | Fraunhofer ISI | director taskforce innovation \ iIndicators |
| Rainer Frietsch | Fraunhofer ISI | deputy head of the competence center |
| Stephan Gauch | Fraunhofer ISI | researcher |
| Thomas Reiss | Fraunhofer ISI | head of the competence center emerging technologies |
| Bernhard Buehrlen | Fraunhofer ISI | researcher |
| Bärbel Hüsing | Fraunhofer ISI | coordinator business unit "Biotechnology and Life Sciences" |
| **Reviewers case study chapters** | | |
| Sibylle Gaiser | Fraunhofer ISI | researcer competence center emerging technologies |
| Martin Hessing | DNC | project manager Nutrigenomics Consortium |
| **Case 1 – Dutch Nutrigenomics Consortium** | | |
| Bernard de Geus | NGI | manager international and project development |
| Martin Hessing | DNC | project manager Nutrigenomics Consortium |
| | NGxC | |
| Michael Muller | WCFS | project leader NGxC |
| Fons Voragen | WUR | director knowledge sciences, knowledge unit agro & food sciences |
| Ronald Mensink | UniMaas | professor molecular nutrition science |

| Interviewee | Organisation | Function |
|---|---|---|
| Niek Snoeij | TNO | director business development |
| Rianne Weggemans | Unilever | scientist cardiovascular health |
| Hans Zevenbergen | Unilever | brand nutrition director heart health |
| Jan Maat | Unilever | director external research |
| Joop Roels | DSM | director strategy & technology |
| Rop Zoetemeyer | CSM (Purac) | director innovations (cto) |
| Joep Sparidaens | NZO (Campina)<br>CMSB | corporate project manager R&D |
| Gert-Jan van Ommen | LUMC | projectleader CMSB |
| Cornelia van Duijn | EMC | coordinator platform epidemiology CSMB |
| **Case 2 – Competenz Network Metabolic Syndrome** | | |
| Pablo Steinberg | Lehrstuhl für Ernährungstoxikologie, Universität Potsdam | director Nutrigenomic Netzwerk |
| Volker Rosenbaum | BioTOP Berlin-Brandenburg | coordinator Nutrigenomic Netzwerk |
| Eva Brand | Medizinische Klinik und Poliklinik D Universitätsklinikum Münster | projectcoordinator MS |
| Annette Schürmann | Deutsches Institut für Ernährungsforschung Potsdam-Rehbrücke Abteilung Pharmakologie | department director |
| Silke Sperling | Max Planck Institute for Molecular Genetics | leader of the research group cardiovascular genetics |
| **Danish Platform in Nutrigenomics** | | |
| Lars Ove Dragsdal DSM/VSOP | Danisch Platform in Nutrigenomics | director |
| Ysbrand Poortman | EGAN/IGA/VSOP | secretary general of IGA |
| Philip J. Rijken, | DSM | head nutritional science DSM food specialties |

# Annex III Example of questionnaire

This is the questionnaire as it was used for the semi structured interviews during the CMS case study. For the DNC a similar questionnaire was used. The questionnaire functioned as a guideline for the interviews. The questions were not asked in a fixed order, but during the interviews it was checked whether all subjects were covered. The questions cover the three building blocks of the FILET and the analytical framework. On behalf of the interviews the questionnaire is structured from a historical perspective. This enabled the interviewees to tell a more natural story instead of jumping back and/or forward between the relations we are interested in. The questionnaire also contained notes (in italics) that could help the interviewer during the interview to recall specific information or events.

***Network formation***

1. Could you tell how the Kompetenznetzes Metabolisches Syndrom was formed? (Who got involved with whom, when and how often?) [i.e. network formation prior to the official start in 08/2003]
2. Who took the first initiative to start the Kompetenznetzes Metabolisches Syndrom?
3. What are the important events during the network formation?
4. What is the key nutrigenomics research area within the network and why this one?
5. How is this related to related other research? developments?
6. And how is this related to the work you normally do in your group?

*Note to self: BMBF grant 0313040A-C, BioProfile Project for the Region Berlin-Postdam"Innovations in treatment concepts for the metabolic syndrome – with focus on hypertension",subproject: "Development of a SNP-based platform for the analysis and diagnosis of hypertension"*

7. Is there a 'translating' intermediary (e.g. who is 'crossing a knowledge gap, since complementary knowledge is brought together) within the Kompetenznetzes Metabolisches Syndrom?
8. How would you typify this intermediary, or what is the most important role of this intermediary? What did he do, when and why?
9. Who was this intermediary?

***Learning process***

10. Which knowledge [what, why, how] was created by which stakeholder and flowed to whom when and why (EVENTS)?
11. Are there after the creation of the Network specific events/crises/triggering events/ external pressures, which influence the learning processes?
12. How would you describe the nature of knowledge in the network (level of concreteness: scientific, development, technical etc.)?
13. Which scientific insights into the Metabolic Syndrome evolved during the Kompetenznetzes Metabolisches Syndrom through which activities (WP's)?

***Learning output***

14. What would you define as learning output for the network? How to show that learning processes actually took place?
15. What is the main network goal regarding outcome/output: creating as much patents as possible, scientific papers output, others?
16. Is this also reflected in scientific papers? Do you have an overview of Kompetenznetzes Metabolisches Syndrom articles? Could I receive copies?
    *I already identified/got two from the info leaflet:*
    - *FUNKE-KAISER H, rEICHENBERGER F,KöPKE K, HERRMANN s-m, PFEIFER J,oRZECHOWSKI H-d, ffIIDEK fi, PAUL m,bRAND e. Hum Mol Genet.2003; 12:423-433.*
    - *KUZNETSOVA t, sTAESSEN Ja, tHIJS l,KUNATH ¢, oLSZANECKA a, rYABIKOV a,tIKHONOFF ff, sTOLARZ K, bIANCHI G,¢ASIGLIA e, FAGARD r, RAND-HERRMANN sm, KAWECKA-JASZCZ K, mALYUTINA s,nIKITIN ffi, bRAND e. Circulation.2004; 110:2644-2650.*
17. Or patents?
18. Or standards?
19. Did you have a shared vision?
20. Did the shared vision act as a driver for learning and innovation?

*Is this the shared vision: PROJEKTZIEL Identifi zierung funktionell relevanter Kandidatengen-Polymorphismen bei Bluthochdruck und Determinierung individueller genetischer Risikoprofile als Basis innovativer nutri- und pharmakogenomischer therapieansätze bei Bluthochdruckpatienten*

***Interaction***

21. Who are your partners?
    - The info leaflet also refers to "*Beratungsunternehmen wird im Auftrag von Ärzten und Patienten sowie Kunden aus der pharmazeutischen Industrie*"; who are they and how are they involved?
    - Relation between the Kompetenznetzes Metabolisches Syndrom and the project Verständnis der Interaktion von Genotyp, Phänotyp und Nahrung für präventive Ernährungskonzepte nutzen [purely medical investigation]?
22. How often do you meet with your partners?
23. Who meets with whom?
24. Are these meetings formal (i.e. planned ahead) or informal (if informal, in which way)?

25. Where do you meet with your partners?
26. How long does it take you to get there?
27. How many people are involved in the network (FTE)?

***Cognitive proximity***

28. What is the technological (e.g. scientific/main research topic) focus of your organisation? Orientation: food, health, other? [essentiellem Bluthochdruck]
29. How would you describe the technological focus of your partners?
30. What are the complementarities between your organisation and your partners?

***Regulatory proximity***

31. Which rules do you have to comply with regarding the research performed for the Kompetenznetzes Metabolisches Syndrom?
32. Is there a mutual agreement/contract between the partners in the Kompetenznetzes Metabolisches Syndrom? (Could I receive a copy?)

- If yes, what is the content of the contract?

***Cultural and social proximity***

33. Do involved actors have a similar or different culture (science or industry => heterogeneity)?
34. Do you share information freely?
35. Do you partners have access to year research facilities and/or knowledge databases?
36. How would you define 'trust'?
37. Do you distinguish different forms of trust?
38. Do you trust your partners?
39. How important is trust for knowledge exchange in the Kompetenznetzes Metabolisches Syndrom?

***Organisational proximity***

40. How would you describe the Kompetenznetzes Metabolisches Syndrom Organisation?
41. What was the budget of the Kompetenznetzes Metabolisches Syndrom?
42. What about the access to scientific, human, material, financial etc. resources in the network?
43. Who financed the network? [via BMBF]
44. What is the relation between Kompetenznetzes Metabolisches Syndrom [i.e. so-called innovation project], BioRegio Berlin/Potsdam Nutrigenomik.de and NuGo?

***Additional info***

45. How do you foresee the nutrigenomics future?
46. Do you have a year report/info on your organisation?
47. Are there any documents that you would recommend for my research on the Kompetenznetzes Metabolisches Syndrom?
    *Since the project ended in 07/2006 there might be an evaluation?*

*Annual reports [determination technological focus => also look at patents and publications]?*

48. Are there any people you would recommend me to interview?
49. Do you know any other national/international nutrigenomics network which could also be studied in a comparative way?

# Annex IV DNC articles

***WCFS and CMSB co-publication:***

Corthésy-Theulaz, I., J. T. d. Dunnen, et al. (2005). "Nutrigenomics: The Impact of Biomics Technology on Nutrition Research." Ann Nutr Metab **49**: 355-365.

***CMSB co-publications:***

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Kreeft, A. J., C. J. A. Moen, et al. (2005). "Genomic Analysis of the Response of Mouse Models to High-Fat Feeding Shows a Major Role of Nuclear Receptors in the Simultaneous Regulation of Lipid and Inflammatory Genes." Atherosclerosis **182**(2): 249-257.

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***WCFS publications:***

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van Ommen, B. (2004). "Nutrigenomics:: Exploiting Systems Biology in the Nutrition and Health Arenas." Nutrition 20(1): 4-8.

# Annex V CMS articles

### *Articles of the Charité-Universitätsmedizin Berlin*


Barbaux, S., D. Tregouet, et al. (2006 submitted). "A System Genetics Approach to Inflammatory Gene Polymorphisms in Myocardial Infarction."

Brand-Herrmann, S.-M., T. Kuznetsova, et al. (2005). "Alcohol Intake Modulates the Genetic Association between Hdl Cholesterol and the Ppar[Gamma]2 Pro12ala Polymorphism." J. Lipid Res. **46**(5): 913-919.

Brand-Herrmann, S., K. Köpke, et al. (2004). "Angiotensinogen Promoter Haplotypes Are Associated with Blood Pressure in Untreated Hypertensives." J Hypertens. **12**: 1289-1297.

Brand, E., J. Wang, et al. (2003). "An Epidemiological Study of Blood Pressure and Metabolic Phenotypes in Relation to the Gbeta3 C825t Polymorphism." J Hypertens. **21**: 729-737.

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# Dankwoord

Promoveren is een proces met een uitkomst. Dit boek is daarvan het meest tastbare resultaat. Maar minstens zo belangrijk, of wellicht nog belangrijker, is het proces dat hier naartoe heeft geleid. Hieraan hebben meerdere personen bijgedragen.

Ellen Moors attendeerde me in 2004 op het NWO promotieonderzoek 'user-producer interactions in nutrigenomics innovations' bij het Departement InnovatieStudies. Dit was dé gebeurtenis die uiteindelijk tot deze promotie heeft geleid. In de tussenliggende periode is Ellen een stimulerende en motiverende co-promotor geweest. Ellen, bedankt voor de goede en leuke gesprekken!

Als promotoren hebben Stefan Kuhlmann en Ruud Smits opeenvolgend complementaire rollen vervuld: Stefan heeft voor verbreding en conceptualisering gezorgd en Ruud heeft dit aangevuld met focus en concretisering. De periodes waarin ik met Ruud het vak Analyse TechnologieBeleid mocht verzorgen waren zeer interessant, vooral door de onconventionele onderwijsvormen. Stefan en Ruud, bedankt voor de samenwerking.

Ik ben mijn collega promovendi (Rob, Simona, Roel, Tessa, Rutger, Ineke, Maryse, Klaas, Laurens, Jon en Sjoerd) erg dankbaar voor de interessante én volledig nutteloze gesprekken. Dit was een optimale mix voor verdieping en verbreding waaruit onder meer het triple C-concept en de FFF zijn voortgekomen ;-) In het bijzonder wil ik 'projectcollega' Wouter (o.s.g.m.w.g.) en kamergenoot Roald (FN-P90) bedanken omdat ze voortreffelijke sparringpartners en uitlaatkleppen waren! De WTMC bijeenkomsten waren even onnavolgbaar als vormend, maar vooral ook erg intiem.

Het scientometrics onderzoek is uitgevoerd tijdens een gastverblijf aan het Fraunhofer Institut für System- und Innovationsforschung in Karlsruhe. Met name Monica, Stephan, Rainer en Ulrich waren erg gastvrij en behulpzaam.

Zonder de medewerking van de experts en stakeholders die geïnterviewd zijn, was dit onderzoek niet mogelijk geweest.

Tijdens de studie Natuurwetenschappen en Bedrijf & Bestuur is de basis gelegd voor waardevolle vriendschappen die zorgen voor reflectie, relativering en heel veel plezier. Het is daarom dan ook heel fijn om te tafelen met Edwin, Nieke, Mattijs, Cindy, Anneloes, Guus, Ellen, Hans, Karin, Jolein, Rebecca, Andreas, Renske en Pieter.

Een fijn en stimulerend thuis – ook wanneer je er allang niet meer woont – is de uitvalsbasis voor elke vorm van ontdekkingsreis (studeren, promoveren, Europa, Amerika, Scandinavië, Zuid-Afrika). Mam, pap en Wies, bedankt!

Gedurende de promotie waren de belangrijkste leermomenten niet of nauwelijks verbonden met het onderzoek zelf. Door de intuïtie en inzichten van dierbaren werden schijnbaar moeilijke keuzes heel eenvoudig gemaakt!

# Curriculum Vitae

Rens Vandeberg (1976) studied Science & Policy at the Faculty of Chemistry and specialised in Sociology at the Faculty of Social Science (Utrecht University). He performed an internship at PricewaterhouseCoopers Luxemburg and after graduation in 2001 (with honours) he worked at Dialogic innovation & interaction. As an innovation advisor he performed innovation projects for (international) companies and governmental organisations. Rens started his PhD research at the Department of Innovation Studies, Utrecht University, in 2004. The research journey into interactive learning in emerging technologies is reflected in this book. Since January 2009 Rens Vandeberg is Programme Officer Nanotechnology/NanoNed at Technology Foundation STW. Here he applies the gained insights into stimulation and management of research collaborations in practice.


Interactive learning has been a central concept in innovation studies since the 1980s and its influence on innovation has been shown in numerous studies since then. Interactive learning is of special importance in emerging technologies like nutrigenomics in which complementary, often tacit knowledge has to be exchanged and combined in order to learn and innovate. However, sufficient insight into the black box of the interactive learning process was lacking thus far.

In this book Rens Vandeberg constructs a Framework for Interactive Learning in Emerging Technologies and explores this framework in nutrigenomics consortia. The developed framework encompasses not only the interactive learning outcome, but also the interactive learning process itself and the conditions that influence the interactive learning process. The resulting insights provide new means for the stimulation of interactive learning, knowledge creation and innovation management.