Biomarkers

as an emerging growth area in Denmark – ideas for innovation and capacity building

White paper
White paper: Biomarkers

This white paper is a result of a collaboration between Biopeople, Bioneer, Brandbase and InfinIT in relation to the project 'Biomarkers as an emerging growth area in Denmark'.

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Chapter 1: Introduction

The Danish economy – in common with the rest of Europe – is in need of new growth areas. Products from emergent industries evolving in the intersections between existing technologies and sectors have been pointed out as crucial to filling this demand.

This white paper presents the results of an investigation into one such emerging industry, that of biomarkers. A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [Strimbu & Travel 2011].

Biomarkers present a promising area for growth for several reasons:

- They represent a strong and growing research area in which new knowledge and insights are being generated at an increasing speed. This promises solid growth potential if new biomarkers can be transformed into useful technologies for doctors and patients.

- The exponential growth of computer technologies, resulting in smaller, faster, and cheaper computers, has created a plethora of portable and wearable sensing devices, from smartphones to wristbands. Digital phenotyping with these devices will provide a large number of new digital biomarkers.

- Biomarkers are anticipated to offer better and more tailored treatment solutions for the individual and improvements in public health through better detection and monitoring.

The partners

Recognizing these perspectives, the project ‘Biomarkers as an Emerging Growth Area’ was developed by three publicly funded innovation networks – Biopeople, InfinIT, and Brandbase – and the life-science focused GTS company Bioneer. The main task of these partners is to support interactions between university-based research and private companies within the life sciences (Biopeople and Bioneer) and within digital solutions (InfinIT). Brandbase, as a fourth partner in these public-private partnerships, contributes a focus on the potential of collaboration with civil society.

The project was co-funded by the Danish Agency for Science and Higher Education with a grant of 3.8 million DKK to Denmark’s Life Science Cluster, Biopeople. The aim was to forward growth initiatives within the area of biomarkers / personalised medicine to leverage future support actions, and to facilitate innovation and new collaborations.

The task

By mapping stakeholders, and engaging in networking activities and ongoing dialogues with researchers, enterprises, and patient organisations, the partners to the project have sought potential sites for public-private-civil co-creation in biomarker development and validation along the value chain from discovery to certification and use.

We have:

- Engaged in dialogues with stakeholders and analysed prominent trends.

- Facilitated dialogues between researchers, patient organisations, and private enterprises within the fields of biotech / life science and digital solutions.

- Investigated industry needs for knowledge, networks, and regulations that may support businesses as they invest time, money, and effort into R&D of new biomarker-based products.

- Searched for innovation potential that may evolve at the intersections of new players and old enterprises; of clinicians, innovative enterprises, and academic researchers; and of civil society and the health care system.

Early in the project, it became evident that some kind of structured sharing of knowledge and identification of evolving challenges was needed if these diverse stakeholders were to realise the potential said to inhere in Danish life science skills, knowledge, and its unique pool of personal data, and in the fast growing field of digital solutions. The role of patient organisations in collaboration, as representatives of civil society, also seemed unexplored and in need of a more structured approach. The importance of these infrastructural requirements was discussed both within the project group and with external stakeholders. This resulted in a number of recommendations which evolved in a series of dialogues between the project group and stakeholders who participated in interviews, debate seminars, and conferences.

The aim

With the aim of supporting the objective of biomarkers becoming a national growth initiative, we here share our recommendations for future capacity building among researchers, developers, and patient organisations at the intersections between the public and private sectors and civil society.
The questions addressed

Chapter 2 consists of a short introduction to the promises and challenges related to biomarkers.

Chapter 3, by Bioneer, presents Danish strengths in the life sciences and the arena of molecular biomarkers. While the latter is in some ways well established, we also encountered a good number of fast growing, small and medium sized enterprises (SMEs) in need of support, regulatory advice and networks.

Chapter 4, by InfinIT, presents the strengths and potential of bioinformatics and digital solutions. The combination of advancements within molecular biology and parallel developments in IT has led to a whole new area of research – bioinformatics – in which Denmark has the capacity for growth and product development. In addition, the enormous pools of personal data being produced through app-based services which individuals are using to monitor their health and health-related behaviour have the potential to generate a multitude of innovative ideas. What can be gained by combining these behavioural and self-reported data with biological health data? And what would it take to execute this? There is definite potential in thinking forward along these lines, and Chapter 4 takes the first step by examining the characteristics of such current digital enterprises in Denmark.

Chapter 5, by Brandbase, focuses on the potential of, and barriers to, collaborating with patient organisations. As biomarker research is both resource consuming yet potentially highly profitable, it is vital to discuss more broadly how medical needs can be identified, how resources should be distributed, how priorities should be set, and how patients can be involved in the research process. Indeed – since the 2000s – patient involvement has become a major and growing moral imperative in the public health sector. Involving patients as contributors of patient knowledge and patient preferences to highly specialized biomedical research and development initiatives is, however, a much less common idea.

Across the three domains we see a number of trends that needs to be addressed if we want to realise the potential of biomarkers research and development. These are discussed in Chapter 6 and form the background for our recommendations for future capacity building activities including the need of an organizing organ, a meeting place and access to knowledge sharing – Chapter 7.
Chapter 2: Background

What is a biomarker – time to extend our understanding?

The modern definition of a biomarker was conceived at a US National Institute of Health workshop in 1998 where it was said, “Biomarkers are objectively measured indicators of normal and pathogenic biological processes and of pharmacological responses to medical treatments” [cited in Strimbu & Travel 2011]. They are classified into different types, based on classical physiological features (like body temperature and heart rate) and molecular traits, which can involve measurement of very specific, highly complex molecular signals in biological samples (e.g., blood and tissue), potentially containing a range of molecules (e.g., proteins, lipids, nucleic acids). On top of that, there is an increasing understanding that external factors associated with lifestyle and environment (known as behavioural or real-world data) also influence the utility and interpretation of biomarker-assisted decision making in healthcare.

The very broad definition of biomarkers provides the potential for their extensive support of not only decision making in disease treatment (the basis for precision medicine / personalised medicine) but also personal preventive health care decisions to ensure the best possible quality of life (QoL) for the individual.

We have defined four types of biomarker sources:

- Data from our genes
- Data from body fluids or other types of biological samples
- Data from biosignals
- Data from behaviour (patterns of movement)

As the list indicates, biomarkers can be biological as well as behavioural in nature. While a large percentage of the research in biomarkers over the years has been invested in biological / molecular biomarker detection, there is a growing trend of combining such research with behavioural data. Through digital analytics, the combination allows for a much more fine-grained picture of the health condition of an individual. Eventually this will lead to personalised medicine.

In the current project we have explored the innovative potential of this trend, a goal that has demanded that we keep a broad understanding of biomarkers in mind, and that we also investigate the borderlines of the more traditional definitions of biomarkers.

The promises of biomarkers

Biomarkers hold out the promise of cheaper development costs for new pharmaceuticals and better treatment, as well as better health. The goals of cheaper development costs and better treatment are embedded in the paradigms of, and considerable investments in, personalised medicine, and have prominent stakeholders within large, established pharma-industries and research institutions, as well as among health-care system policy makers.

The promise of better health is partly catered to outside the health care system where start-ups and SMEs are providing new services due to smaller, faster, cheaper, advanced technologies, enabling the empowerment of the users / patients through, for instance, intelligent wearables and cheap access to advanced cloud analytics.

The potential of biomarkers for drug development and better treatment

Drug development is a very expensive and complex process. Of the total number of new drugs, that go into precious preclinical developmental stages and clinical trials today, more than 90% are not finally approved (Thomas et al. 2016). At the same time, there is an ongoing need for the development of new and better treatments, not least in oncology, where the overall treatment efficacy of major drugs is only 25% (Spear et al. 2001). In general, within the more complex diseases, the era of “blockbuster” drugs, developed for the mass public, is long gone. To increase the success rate of new drugs, pharma is increasingly recognizing that new drugs must target smaller groups of patients, with the ultimate aim of designing treatments for each individual patient – personalised medicine. To accomplish this the use of biomarkers is of growing importance.

Today, molecular biomarkers are more extensively used in the early drug development process: to elucidate the mechanisms of drug action, for example, and to help evaluate the efficacy of drugs relative to dose and unintended toxic effects. In clinical trials testing new drugs, analysis of biomarkers in the patients involved is also being used as a basis for evaluating the clinical effect of the drug. This is particularly the case in relation to many of the new targeted therapies, where a pre-selection of patients with a preferred biomarker profile can enhance the chance of producing an acceptable improvement in treatment efficiency.

Because of the acknowledged benefits of biomarker identification, the development of drugs and the deployment of biomarkers today walk hand in hand. It is predicted that this trend will become increasingly important due to strict-
Sensors can be used to collect data in our environment, on the body and maybe inside the body. Smartphones have a built-in range of sensors that may be used to measure behaviour biomarkers in particular. The cloud is a name for a network of attached datacentres that can store and analyse huge amounts of data, referred to as big data. These developments open up innovative ways to collect, use, and identify biomarkers for the improvement of health. With a smartphone in the pocket citizens can be connected to a global market of health services that is growing exponentially. Combined with the achievements within health science in recent decades, these technological advancements create exceptional opportunities for developing digital services within prevention, diagnostics, and treatment, based on the individual citizen’s biology and needs. Further digital technologies can also be used to find and evaluate data regarding biomarkers. By using artificial intelligence and machine learning to identify correlations in vast quantities of data, it is possible to identify patterns which are completely new as well as patterns that could constitute new biomarkers. The technological developments also affect the interplay between actors in the sector. For many years the health care sector has been the primary buyer of health IT solutions in Denmark but now private companies are also offering citizens digital health services directly. This requires reorientation in how citizens, health care professionals, and private companies interact and collaborate. Why invest in biomarkers?

With the essential need for biomarkers to support both preventive and disease-associated healthcare, there is a huge market potential for new biomarkers. Several Danish companies are already addressing this market with innovative technologies, particularly in the area of disease diagnostics. Such companies that we interviewed expect substantial growth both in numbers of employees and turnover within a timeframe of five years. Danish companies are thus aligning with international expectations of growth within the field of biomarkers. The worldwide information services company, Global Information Inc., has in their market research report on biomarkers forecast that ‘[t]he global market for biomarkers should grow from $78.9 billion in 2018 to $136.5 billion by 2023 at a compound annual growth rate (CAGR) of 11.6% from 2018 through 2023’
Similarly, Allied Market Research Inc. expects the global biomarker market for diagnostic applications to garner $30.6 billion globally by 2020, registering a CAGR of 16% during the forecast period 2013 to 2020.

In short, investments in biomarkers promise not only health and societal advantages but also commercial growth.

The challenging translation of biomarkers from bench to bedside

While research on thousands of new potential biomarkers (especially molecular biomarkers) is continually being published, only a few of them have been validated for clinical usage; to a high degree this is due to the lack of standardised analytical methods and commonly accepted criteria for validation (van Gool et al. 2017), but the translation into clinical use is also filled with implementation barriers (Zineh & Huang 2011).

Another important barrier in the translation of biomarkers from bench to bedside is the time factor. Stakeholders, along the road from early discovery through the development of tests that must then be validated before a drug is finally used by patients and doctors, may each have good reasons for doing what they do at their own point in the journey. Seen from a patient perspective however, the smooth translation and speed of the entire process matter the most. Consequently, collaboration with patients whose interest lies in pushing the process has been pointed out as key to speeding up the translation from bench to bedside. At the same time, patient involvement may support prioritisation; by listening to patients, R&D may be better directed towards end users’ perceptions of which products are most needed, which again may lead to more relevant and hence more applied products (Novas 2006, Callard et al. 2011). However, despite the hopes attached to patient involvement, only a few stakeholders have practical experience of such collaborations.

If we look at the digital arena, we find fast growing pools of data on human behaviour and human illness both within and outside the health care system. These datasets provide the potential for analyses on an aggregate level that may both detect patterns relevant for the discovery of new biomarkers and increase our knowledge on the links between factors like health, illness, treatment, and lifestyle. However, this potential demands that these digitally layered data are not only used to monitor the individual, as is most often the case today. Furthermore, if data are to be used in future analytics, a range of translational questions needs attention.

It is apparent that challenges to the translation of biomarkers from early detection and development to useful end products are numerous. In the following, we address these translational challenges in depth, and provide recommendations for a way forward.
Chapter 3: Biomarker potential from a life science / biotech perspective

Introduction
The drive towards implementing the concept of personalised / precision medicine is receiving tremendous attention globally and nationally. The use of biomarkers is key to this development, and awareness of the use of biomarkers to aid in drug development, improved disease diagnostics and treatment, early detection, and prevention of diseases, has become increasingly widespread in both healthcare systems and the pharma industry. However, the development and validation of biomarkers for clinical use is a complex matter and, depending on the type of biomarker(s) in question, requires a multidisciplinary effort involving molecular technologies, bioinformatics, and access to patient material, among other things.

Aim
The purpose of this chapter is to map Danish strengths and views on biomarker development and exploitation from a life science perspective, employing contributions from biotech and pharma, and input and perspectives from researchers and clinicians. A parallel purpose is to identify potential challenges and barriers for continued and optimal development of biomarkers in Denmark.

Method
The chapter is based on expert interviews with 15 different Danish stakeholders positioned in different parts of the biomarker development value chain. The interview team consisted of an experienced R&D manager within molecular biomarkers and a business executive with experience in research policy and funding, who engaged in dialogues with the experts using an open-ended approach guided by a list of questions to ensure that the same aspects were discussed every time.

In all the interviews, beyond identifying specifically Danish strengths and strongholds, there was a special focus on identifying and discussing potential challenges and barriers to, and requirements for, the efficient development and exploitation of biomarkers. In the last part of each interview session, we discussed the idea of establishing a biomarker development infrastructure as a national initiative, to provide access to the necessary skills to drive the development of biomarkers in an efficient way. This idea was proposed and elaborated on by the project partners as a result of our cross-disciplinary engagement throughout the project and much inspired by the Dutch Health-RI initiative [see www.health-ri.org]. The views on such an initiative are reported in the recommendations of the white paper (Chapter 7).

The interviews were conducted with 11 life science companies, both pharma and biotech, one biobank, one university department and two clinicians in oncology and rheumatoid arthritis, respectively. The interview with the Danish National Biobank (Danmarks Nationale Biobank), which represents an important source for coordinating access to biobank registers and clinical samples in Denmark, placed considerable emphasis on regulations governing the sharing and accessing of clinical samples for biomarker development. The interview with the Department of Pharmacy at University of Copenhagen focused on increasing the general awareness and knowledge of regulatory issues in relation to biomarker and drug development. Finally, the interviews with the two clinicians provided valuable insights into the practical use of biomarkers both in the standard of care routines and in clinical research.

In the following, we have extracted the information from each of the stakeholder interviews that has relevance for mapping the Danish landscape of biomarker development and validation by listing both strengths and challenges as expressed by the participants.

Limitations
The selection of the participants invited for the interview series was based on an internal listing and preliminary evaluation of companies and other organisations with potential interest in biomarkers. The internal listing comprised approximately 30 companies / organisations from the life science sector in Denmark and selected from members of the Danish Biomarker Network. In comparison, Dansk Biotek has approximately 100 company members, which cover life science / biotech interests more generally. After evaluation of the internal list, approximately 20 invitations to specific stakeholders were mailed with a positive response rate of 75%.

We are aware that this is not an exhaustive list of all the potential stakeholders in biomarker development and interests in Denmark; however, we believe that the participating companies and organisations represent a sufficient and valid distribution of stakeholders with interests in biomarkers and biomarker development across the entire value chain from early discovery to validation and clinical implementation.
Types of companies and their characteristics

Two categories of companies have been interviewed: Biotech and Pharma.

Biotech: The biotech companies are almost all characterised by being SMEs (seven of eight) with between three and 55 employees (the majority in the range of 5-20). Agilent Technologies, formerly known as Dako, is part of an international company and considered a large entity. Two of the companies were established in 2017, while the others have existed for between four and 16 years. The eight companies are technology-focused, offering diverse solutions for biomarker analysis including discovery, visualisation, validation, and in silico computational methods. A common feature of views in the biotech industry are challenges in accessing the public health care system.

Pharma: The three pharma companies, two large and one SME, operate in different disease areas. The importance of biomarkers in the modern drug development process were discussed. Characteristically, Ferring and LEO Pharma, which both provide health care solutions for normally non-life threatening diseases, have only recently raised the awareness of the use of biomarkers in their drug development programmes. Symphogen, an oncology-focused pharma company, is actively pursuing the potential benefit of including biomarkers in their drug development programmes. The pharma companies have all become aware of the importance of including biomarkers to improve treatment outcomes.

Danish potentials and strengths in biomarker development and validation

Potentials and strongholds anchored in Danish biotech enterprises

Denmark has a wealth of biotech-based SMEs that in some cases offer unique and state-of-the-art technologies in niche areas supporting the development and validation of biomarkers. In the non-exhaustive list of companies that we have interviewed we want to highlight a few of these. The three examples below are characterized by offering products, technologies, and solutions within the biomarker field that stand out compared to competitors even on a global scale; all have great prospects for future advancement, growth, and consolidation.

Visiopharm is developing image analysis software for digital pathology applications, with a primary focus on supporting pathology core units, biopharmaceutical companies, and tissue biomarker developers. The computational technology not only offers automated solutions for higher throughput, but also a radical approach to improving data quality and interpretive accuracy. The technology is based on proprietary image analysis and artificial intelligence / deep learning, and integrated with lab information systems, picture archiving and communication systems, and image management systems to support lab workflows. Cancer tissue-based diagnostics is the primary market for Visiopharm. With more than 600 targeted treatments in late stages in the pipeline worldwide, they believe there is a growing need and demand for accurate identification of responders via new and improved tissue-based diagnostics, through multiplex analyses and determination of context-based parameters in the tumor microenvironment – especially in relation to the many new and emerging cancer immune therapeutic treatments. Visiopharm shares a widely held view that companion diagnostic biomarkers are a prerequisite for developing a sustainable healthcare system, based on precision medicine. Tissue pathology is an important component in providing meaningful predictive tests but in the current healthcare system, the pathology function often represents a bottleneck. Visiopharm is the global technology leader in image analysis technology for tissue pathology, providing tools that augment pathologists.

Intomics is an in silico bioinformatics company that offers solutions for the analysis and interpretation of large amounts of biomedical data (typically x-omics data) to pharma and biotech companies globally. Its offerings are based on the combination of applying advanced algorithms, in-house
on bioinformatics and advanced digital image processing algorithms. Some companies offer established technologies like mass spectrometry and in-licensed proteomics platforms as service providers, while others are developing their own technologies and solutions to improve the current state of the art. Many of the companies have established intellectual property rights over their products and, hence, can offer unique solutions on a global scale.

In conclusion, the capacities that are anchored in Danish biotech companies have the potential to be involved in a dedicated initiative to utilize the potential of biomarker development and validation in Denmark, depending on the type or types of biomarkers in question.

Other organisations with potential and strengths for biomarker development

In our efforts to identify the cornerstones of Danish biomarker development, we identified two existing organisations that have established expertise central to the biomarker development process.

An essential component in biomarker development is access to biological material from patients and healthy controls. In Denmark, the Danish National Biobank (DNB) has been established to coordinate records of 24.5 million biological samples from the entire country, including tissue biopsies and blood samples from a range of diseases in different hospitals. The ambition of DNB is to enrol other biobank resources within Denmark, from the CopLab for example, that contain records and 172 million biological samples from GPs in the Copenhagen area. The DNB initiative potentially represents a leading global resource for biomarker development. Through the web portal, forskerservice.dk, not-for-profit researchers can apply for access to biological samples or data from selected patient groups. The Danish data-protection agency and a scientific committee associated with DNB – including representatives from the Independent Research Fund Denmark (DFF), the regions, and Danish patient organisations – will assess and approve the applications within 30 days.

Another important element in good biomarker development practice is attention to standardization and regulatory issues. In our interview with the Department of Pharmacy at Copenhagen University, the subject of the newly established Copenhagen Centre for Regulatory Sciences (CORS) was discussed. CORS is a collaboration between Danish pharmaceutical industry partners (LEO Pharma, Novo Nordisk, Lundbeck, and Ferring), the Danish Medicines Agency, and the University of Copenhagen (Dept. of
Pharmacy). The vision of CORS is that it will assist in the creation of structures, activities, and collaboration models through research and education that will ensure that drug and biomarker validation is conducted to the highest standards, with the most relevant analyses, using the best available materials, and in full compliance with regulatory requirements. CORS has the ambition to become a global leader as a regulatory centre focusing on standards and mind set within a 15-20 year period.

The Danish National Biobank and CORS represent existing infrastructural institutions that should obviously be included as part of a more dedicated initiative specifically focusing on exploiting the potential of biomarker development and validation in Denmark.

The perspective of large pharma companies

We supplemented the identification and mapping of Danish biotech-focused initiatives – those relevant to biomarker development and validation – with the views of three pharma companies on the status of the use of biomarkers in their respective contexts.

Lars Karlsson, Executive Director of Translational Medicine at Ferring, explained that the need for biomarkers must be evaluated in relation to the specific indication and type of drug under development. In life-threatening diseases like cancers, biomarkers predicting treatment benefit are of high value, but most of the diseases in Ferring’s focus are not life-threatening, and the benefit of predictive biomarkers is often less clear. Ferring follows a ‘readiness and awareness’ approach with regard to the need for biomarkers during preclinical and translational development, and will only fully commit to the development of a CDx if there are convincing reasons for doing so.

Symphogen, which has an oncology focus, recognizes the strategic importance of biomarkers for future drug development, stating that biomarkers should be taken into consideration very early in drug development. Consequently, they are now routinely taking blood samples of all patients in clinical trials. Symphogen’s next lead is Sym015, targeting the MET-receptor of tumours; it is essential to select patients (stratification) with an amplification of the MET gene to improve the likelihood of treatment success.

LEO Pharma has worked for several years with both the unbiased and hypothesis-driven use of biomarkers for the detection of signalling pathways involved in psoriasis and atopic dermatitis, for example, and also to improve understandings of disease and the mode-of-action of investigatory drugs. Most dermatological diseases are not life-threatening, the effect of medication on the disease is usually visible to the naked eye within few weeks of treatment, and traditional therapies have not been targeted, which has meant less focus on improvement of patient stratification methods within this disease group. LEO Pharma has recently moved into the development of targeted biologics drugs, which are expensive but may be highly efficacious in a subset of patients. Therefore, since 2016, LEO Pharma has been focusing on biomarkers especially in relation to the stratification of patients.

It is interesting to hear the views on biomarkers in relation to drug development described here by three different pharma companies. Clearly, there is a difference in their opinions on the importance of biomarkers, a difference associated with whether they address life-threatening or non-life-threatening diseases. In the oncology field in particular, in which Symphogen operates, there is considerable focus on, and awareness of, biomarkers, governed by stricter regulation and demands for accompanying diagnostics to guide treatment in oncology. However, it is also interesting to note that although companies like Ferring and LEO Pharma do not address life-threatening diseases, they have both invested resources in activities related to the use of biomarkers. In fact, Ferring was involved in bringing one of the first non-oncology associated CDx assays into the market, measuring the level of the female hormone AMH prior to initiating fertility treatment with the Ferring drug Rekovelle. This makes it clear that pharma companies developing drugs for non-life-threatening diseases are also investing effort in investigating the usefulness of biomarkers to improve treatment efficacies, for example.
Challenges and barriers for efficient biomarker development and validation

Some of the same challenges and barriers to the development and validation of biomarkers appear across the range of enterprises, some more frequently than others. Below we have extracted a list of specific and common issues, concerns, and challenges raised by the different stakeholders in relation to efficient biomarker development and validation, seen from the industry point of view (biotech and pharma).

- The entire regulatory landscape in terms of obtaining approval for IVD products is the biggest barrier to technology development. The company Agilent is experiencing stricter requirements for product approval from the FDA, and increasingly also in China and Japan; meanwhile, EU legislation in this area is being redesigned (going from IVD to IVDR regulation), which will also tighten the requirements in the approval procedure.

- It is widely believed that tissue-based testing, with its ability to accurately describe the tumour microenvironment and provide contextual information, will be a necessary complement to gene sequencing / molecular diagnostic approaches in order to realize the vision of personalised medicine. As Visiopharm expresses it, a much wider palette of biomarkers needs to be taken into consideration, providing ‘data-layers’ that collectively provide a more accurate understanding of individual patients. Visiopharm recommends stopping silo thinking, instead focusing on a more holistic approach towards the implementation of personal medicine, which most likely would also ease the clinical implementation of new biomarkers.

- It is hard to raise funding for biomarker development.

- In relation to achieving ISO 13485 certification, PentaBase has experienced major challenges in gaining access to ‘notified bodies’ [like TÜV and Lloyds] in Denmark with the correct codes for CE-IVD approval of products. Similarly, 2cureX sees big challenges in gaining access to hospitals / clinics, and in regulatory issues related to achieving CE certification.

- Access to tissues, biopsies, surgical sections, etc. has become increasingly difficult. For instance, Agilent is now almost entirely dependent on a few foreign commercial suppliers, from whom they buy clinical tissue with only the most basic background data. The biggest problem is access to tissue samples for the rarest cancer types. Biobanks are not much used, because only a limited amount of tissue can be obtained from that source.

- The cost of carrying out the validation of biomarkers is huge, and small technology-focused companies such as MethylDetect cannot undertake such a project alone. Ambiguous regulatory issues and problematic access to patient material are critical challenges in the validation process.

- The IPR situation in relation to biomarkers has changed. Today, it is unlikely that IP will be granted on biomarkers merely on the basis of preliminary evidence of the biomarker’s clinical utility. As Tomasz K. Wojdacz (MethylDetect) expresses it, this is because, previously, patent applications were filed without sufficiently solid underlying data. The lack of strong clinical evidence and insufficient documentation of a given biomarker’s clinical validity means that no one (typically from the pharmaceutical industry) wants to invest in further development of the biomarker, including patenting costs. This situation is often related to the inadequate experience of researchers and university tech transfer units with industry demands when assessing biomarker-related IP.

- Several companies mentioned problems with IP legislation and doubts about ownership (researcher or university), as well as the TTO’s difficulties in assessing the value of patents, signing agreements with sufficient speed and realising reasonable upfront distribution of rights. One unsolved complication is that, to date, only single biomarkers have been patented while the real need is for panels and complementary sets of biomarkers. If IP value is assessed individually, the total cost for biomarker panels or sets may prohibit their use, especially for smaller companies.

- Development of CDx assays for FDA approval is a huge challenge.

- It is difficult to achieve sufficient robustness in biomarker validation testing.
The challenges and barriers listed here illustrate the number of different kinds of issues and concerns to tackle before being able to fully exploit the potential of biomarker development and validation from the point of view of the biotech/pharma industry. Many express concern about the challenges associated with getting regulatory approval for new products due to changing and tightening legislation both in the EU and in Japan and China. Others see challenges in raising the awareness of the use of biomarkers beyond the current focus on genes and molecular diagnostics. Another fundamental issue mentioned by several of the stakeholders relates to the problem of financing biomarker development, which is also linked to the difficulty of obtaining IPR on biomarkers because of a lack of solid supporting data on clinical utility. General difficulties in getting access to clinicians were also mentioned. Finally, several of the stakeholders talked of the challenges and difficulties in gaining access to biological samples (e.g. tissues and blood) with clinical relevance. In conclusion, it is apparent that a number of challenges and barriers to biomarker development are common among different stakeholders, and a dedicated initiative to circumvent and improve these issues would provide a better basis for biomarker development in Denmark.

**Taking biomarkers from validation to clinical implementation**

Hospitals, clinicians, and GPs who represent the Danish healthcare system, recognize the potential of utilizing biomarkers and are also important stakeholders in biomarker validation and implementation. In our interview series, we discussed the status of the use of biomarkers in standards of care and clinical research with two clinicians.

Professor Bent W. Deleuran evaluated the status of biomarker application in regard to the autoimmune disease rheumatoid arthritis (RA). Within RA, there has been a change in culture in recent years in the practice of GPs, which has resulted in greater awareness of the early symptoms of RA (e.g., onset of joint pain), which has markedly improved treatment efficiency, because early discovery of the disease and improved treatment efficiency go hand in hand. The early diagnosis of RA is also supported by biomarkers. High levels of IgM-RF and anti-CCP in the blood are indicators of a poor prognosis and therefore need for intensified treatment. 60% of RA cases are attributed to hereditary factors. For RA, there are no approved CDx assays, but antibody-based therapies are typically offered as second line treatment that is guided by measurement of particular biomarkers. For instance, retuximab, which is an anti-TNFα antibody, is only administered to patients with high levels of RF, while toziluzumab is prescribed for those with high C-recreative protein levels. In addition, Bent W. Deleuran’s own group has had very good experiences with measuring CXCL13 using a CE-IVD-labelled ELISA kit. This assay indicates the presence of dendritic cells, considered a mechanical biomarker for RA, and can be deployed early in the course of the disease.

Professor Ulrik Lassen, clinical director of the Department of Oncology at Rigshospitalet assisted us in evaluating the use of biomarkers in cancer treatment. The standard of care in the clinic is highly regulated, and only validated and approved biomarkers are routinely used. These include subtyping breast cancer patients with ER/PR/HER2 biomarker status to guide treatment options, and measuring blood markers like carcinoembryonic antigen – an important prognostic marker in colorectal cancer and genetic mapping of, for example, BRCA and KRAS mutations – which also guide treatment decisions. In clinical research, the use of omics technologies (DNA sequencing: exome and whole genome) is a state-of-the-art method of characterising the individual patient. The continuous growth in data generated by these methods, coupled with clinical end-points, represent a very important resource for identifying biomarkers that can help improve the prediction of the risk of relapse after surgery, and enhance the ability to predict the best possible treatment. In cancer therapy, there is also considerable focus on emerging immune-checkpoint inhibitor treatments (e.g., PD-L1 inhibitors) and on trying to identify the key to the efficacy of these therapies, because, while these new therapies have given hope to many cancer patients, there is also evidence that they can cause terrible side effects. The use of biomarkers is indispensable in this context.

In summary, the statements from these two clinicians illustrate end-user awareness of biomarkers and their readiness both to utilize biomarkers as an important tool in their daily work, and to contribute to improving the use of biomarkers.
Barriers to clinical validation and implementation

From the clinical perspective, a number of issues and concerns are raised in relation to biomarker validation and implementation in clinical practice:

- When biomarkers are implemented to support diagnosis, prognosis, and choice of treatment, their validation becomes very important. There is a need for a common agreement on e.g. how many false negatives / false positives are acceptable; or, in other words, how well a biomarker must work before it is a useful indicator in a clinical context.

- There is a need for new and more precise methods to predict the treatment outcome that the individual patient can expect, methods based on statistically proven knowledge gained from the traditional randomized controlled trials. We need methods that take patient heterogeneity and lifestyle factors into account, and while such methods may build extensively on biomarkers, they must also involve other factors that may conceivably affect treatment.

- International collaboration / networks and large randomized trials are prerequisites for the validation of new biomarkers, as Denmark is too small in itself to be able to complete the necessary validation process.

- A major barrier to the qualification of new biomarker candidates in the clinic is the lack of population data because Denmark lacks a system whereby the number of patients to be enrolled in experimental treatment can be managed and increased. A cultural change is required to begin enrolling patients in experimental treatment.

- Another barrier is the lack of time resources on the part of clinicians to invest in experimental validation, due to their daily workload.

Clearly, the issues and concerns raised by the clinicians are not simple to resolve, and they call for somewhat radical changes in the way patients can become involved and be offered the opportunity to participate in experimental treatments. Another fundamental issue – the absence of a common and uniform definition of criteria that a biomarker must fulfil in the clinical context – will require that all relevant stakeholders in the biomarker development value chain come together to establish a forum in which to discuss the topic and reach agreement on common guidelines.
Chapter 4: Biomarker potential from a digital/IT perspective

Introduction
The combination of advancements within molecular biology, and parallel developments within IT and digital solutions, has led to a whole new area of research – bioinformatics – that holds the potential for growth and product development in the field of biomarkers. In addition, the enormous pools of personal data generated by wearables and app-based services, whereby individuals can monitor their health and health-related behaviour, provides tremendous scope for innovative ideas. In this chapter we investigate this potential from a digital perspective.

The potential of bioinformatics in biomarker development
Spearheaded by the groundbreaking chemical and physical advances in genomic sequencing, and the publication of the Human Genome (International Human Genome Sequencing Consortium 2001) only one and a half decades ago, a revolution in the use of ICT and digital technologies has quickly allowed genomic sequence data to become a unique source for value creation in many dimensions – most notably for further research, translation of data into biological function, and (integrated with phenotypic data) also in diagnostic and therapeutic applications. Many areas of technology fused together in this accelerated evolution of the new bioinformatics discipline, which has also rapidly led to a growing commercial market, along with genomic sequencing.

Bioinformatics is an interdisciplinary field of science that develops methods and software tools for understanding biological data. As such, it combines biology, computer science, information engineering, mathematics, and statistics to analyse and interpret biological data. Bioinformatics has been used for analyses of biological queries applying mathematical and statistical techniques.

This is one of history’s most conspicuous examples of technology conversions between ICT / digitisation and biology / health – often called the BioIT revolution – and together with the use of a broad array of non-genomic biomarkers it has led to the promise that the personalised medicine concept will provide the basis for a more sustainable public health system (efficacy, patient benefits, quality of life (QoL) and cost).

Denmark has a leading position in the field of bioinformatics, in both research and business development, which can be attributed to many driving forces including:

- The unique health data registry system (CPR-based) linked to patient medical records, and national disease and death registers facilitating national level studies of health-promoting factors as well as disease aetiologies.
- Some of the world’s best and longest running clinically described patient cohorts and associated biobanks.
- Leading research groups in biological sequence analysis and bioinformatics (DTU, KU), AI and Machine Learning (DTU, KU), and pervasive computing (AAU, DTU) and end-user involvement (the Alexandra Institute).
- Important research centres such as the Bioinformatics Centre, at the University of Copenhagen.
- Strong scientific and technical collaboration with the globally leading genome sequencing and bioinformatics company, Beijing Genomics Institute which has its European headquarters and labs in Copenhagen.

Denmark’s bioinformatics companies include:

- Clinical Microbiomics that does microbiome research from experimental design to final analysis and interpretation on a contract basis.
- DNASense which produces microbial community amplicon analysis packages, genome and metagenome sequencing packages, and transcriptomics packages, as well as providing consultancy on bioinformatics projects.
- Intomics described in the previous chapter, which specializes in deriving core biological insights from the analysis and integration of multi-omics and other biomedical big data.

In short, bioinformatics in Denmark is a research field that reaches out into the private sphere; it has infrastructure for gathering and storing data, the potential to combine large sets of different health-related data, and access to the latest advances within micro-/biological and computer science research. Consequently, we see a strong potential for future innovations within bioinformatics and related fields.

Parallel to developments within bioinformatics, new kinds of data-based products and companies are emerging: For example Enversion A/S which has supported analyses of late complications of breast cancer, reported on factors such as drug consumption and telemedicine, and monitored patient history; and Qampo ApS that translates complex datasets into options enabling intelligent choices, based upon mathematical modelling and AI, and is listed on several rankings of new companies with disruptive potential.
This area of growth and the new kind of digital biomarkers that accompany it has attracted our particular interest in the current project.

**The emergence of digital biomarkers**

The spread of wearable digital technologies that generate data has entailed the appearance of a new type of medical information in healthcare. These data produce actionable insights into the biological state of individuals, just like molecular biomarkers, but are collected through and with digital tools; digital biomarkers have the potential to play an important role in the transition towards personalised medicine. Internationally, we have seen a rapid growth in the number of fitness trackers, step counters, health apps, sleep sensors, pocket ECGs, and other health-parameter-measuring devices in recent years. The most well-known example in Denmark is perhaps the fitness tracker Endomondo, now owned by Under Armour, while the most prominent players in the global market are Apple with its Health Platform, Samsung with Gear Series, Fitbit with fitness trackers, and Xiaomi with the Mi Band wristband. All have a strong focus on health and an active lifestyle. At the same time, we also see a plethora of smaller companies such as MOCACARE, NeuroMetrix, Ginger.io and Glooko that monitor and analyse different physical and mental states in relation to conditions and diseases, such as diabetes, low blood pressure, Alzheimer’s, and mental illnesses.

**Aims**

This rapid international development has revealed a need for an exploration of the current situation in Denmark. What companies are dealing with this emerging field? What are they doing about it? How do they approach it? What digital technologies are they using and with what ambition? We have tried to answer some of the questions by mapping digital biomarker companies in Denmark. In the next section, we provide an overview of the mapping process and how it was conducted; then we describe the results of the mapping; and in the final section, we discuss the findings from ten interviews done with companies identified during mapping.

**Method and limitations**

We began the mapping in the autumn of 2017. The purpose was to identify and characterise Danish companies that either have developed, or are in the process of developing, IT-based products that include the use of biomarkers as a substantial part of their service offering. As the field of digital biomarkers is an emergent one, we chose an open approach, seeking companies that are working with discovering, collecting, and analysing general and digital biomarkers. To identify companies, we primarily used Google’s search engine. We began by creating a list of different keywords that can be associated with general biomarkers, such as blood sample, brain scan, rehabilitation, and personalised medicine, that we – in most cases – combined with technological keywords such as machine learning, IoT, smart device, and wearable. Following the search results from these queries, we inspected company websites and read product descriptions and newspaper articles. Whenever we came across a company that matched the above-mentioned criteria, we added it to a spreadsheet list. We are well aware that this approach probably does not provide an exhaustive list of all relevant companies. However, we do believe the findings can be used as a first step towards understanding which companies in Denmark consider the biomarker field a business area and how they approach it. In total, 48 companies were identified. The next step of the mapping was to characterise the companies and the services they offer based on the following properties: corporate form, type of biomarker, business area, customer segment, data sources, and key activities.
Findings from the mapping

Copenhagen-based start-ups dominate the picture

We began the categorisation of companies by looking at their corporate form and geographical location. This showed that more than two-thirds of the identified companies were either micro (<10 employees) or small companies (<50 employees). We also found that a large number of the companies had been founded within the past 3 to 4 years. In other words, many of the identified companies are start-ups that have been ‘born’ in the field. If we look at some of the medium-sized companies on the list, two established insurance companies, Tryg and Top Danmark, stand out. From news articles we learned that both companies are exploring new types of insurance that will offer customers a lower price on their premiums if they agree to share data about their health and level of physical activity. However, neither company has such a service on the market yet. Other examples are IBM Watson Health that has established collaboration with the Rigshospitalet on the use of artificial intelligence to assist oncologists in their work, and LEO Pharma Innovation Lab that – among other services – offers the MyPso app that helps people living with psoriasis to manage their condition. In terms of geographical location, most of the identified companies, again two thirds, are located in or near Copenhagen. The remaining third is located in different medium-sized cities across Denmark, with the second largest concentration of companies in Aarhus (5 out of 48). Based on this, we can conclude that Copenhagen-based start-ups seem to dominate the picture.

A wide variety of biomarker-based services and products

To characterise the companies’ services, we categorised each of them according to the following four parameters: biomarker area, business area, customer segment, and product type. To categorise biomarker areas, we have used the four areas of biomarkers described in the Introduction to this white paper:

- Data from our genes
- Data from body fluids or other types of biological samples
- Data from biosignals
- Data from behaviour (patterns of movement)

The categorisation shows that 20 out of 45 categorised companies, almost half of those identified, are working with behavioural data: eight are working with biosignals, ten with genes, and seven with body fluids. (Note: three of the identified companies have not been categorised due to lack of information about their services.)

One reason for this difference could be that behavioural data are often easier to collect as smartphones have built-in sensors that can record behavioural data such as activity levels and sleep patterns. Companies working in the other biomarker areas often rely on a physical device and/or a test to collect data.

Figure 1:
Number of companies working with the different biomarker areas

In terms of business areas, all the companies are associated with healthcare in some way. But when we looked more closely, we saw a wide variety in the themes on which the companies focus, ranging from monitoring mental well-being at work (Resilio) and automated analysis of MRI scans (Cercare Medical) to assisting clinicians in risk-profiling potential cancer patients (BiomediQ). This variety led us to look at whether the companies’ services address a specific condition or are more focused on lifestyle and health in general. This categorisation showed that most of the companies’ products address specific conditions; only five of
the 45 categorised companies focus on lifestyle and health in general. One of these is AthGene, which uses a genetic home test kit to provide their customers with advice and guidance on how to improve their health based on their genetic profile. Another example is Quarasense, which has developed an app-based service around a unique menstrual pad that is able to detect biomarkers such as hormones, vitamins, high risk human papilloma virus (HPV), and other disease markers in menstrual blood, informing women about their health in general based on these data.

Regarding customer segments, the categorisation shows that half the companies target private individuals, while the primary customer segments of the other half are health care professionals.

To further characterise the companies, we also looked at product type: whether they offered a service product, a physical product, or a combination of the two. The categorisation shows that 26 companies offer a service product, five companies a physical product, and 14 offer a service that includes both. An example of a company in the first category is Twinbody, which offers a social weight-loss app that enables users with the same body type and fitness goals to connect and support each other in achieving a healthier lifestyle. Another example is FindZebra, which has developed a deep learning-based decision support system intended for physicians and other professionals concerned with diagnosis of rare diseases. Twinbody’s and FindZebra’s offerings are very different from each other but are both examples of software-based services. One of the companies that offers a purely physical product is Cortrium. They have developed a digital and wireless ECG monitor that healthcare professionals can use to screen patients for heart arrhythmia. Even though Cortrium’s service includes software to set up the device and to transfer data from the device to a computer, it is the hardware part that differentiates the product. An example of the third category is IctalCare, which offers a service called EDDI to people who suffer from epilepsy. EDDI consists of a physical sensor that is mounted on the body and registers when an epileptic seizure is coming, notifying relatives or caretakers through a receiving device.

Figure 2: Number of physical, physical/service product, and service products.

Clustering digital biomarker companies

Whether the data the companies use to deliver their services come from a sample, a sensor, or other sources, they play an important role as key resources in the business models of the companies. At the same time, the way the companies process these data is an equally important component of the service delivery. It is a key activity in the companies’ business models.

In order to understand what the companies can be said to ‘do’, we clustered them based on how they collect and process data. First, we looked at the 45 companies’ data sources, finding that their services can be grouped into four categories, based on:

- Manually entered data – 9 companies.
- Sensed data – 21 companies.
- A sample or test – 6 companies.
- Data provided from other sources – 9 companies.

Secondly, we looked at how the companies process and handle data. Here we found that the companies’ services can be grouped into three categories:

- Measuring services to determine some sort of value or amount – 7 companies.
- Monitoring services to determine the status of a condition, an activity, or a process at different stages or different times – 19 companies.
- Services that perform some sort of automated analytics on collected data – 18 companies.
If we combine these two aspects of the companies’ business models, we get a 4x3 matrix, as seen in Figure 3. That can be used to derive five clusters of digital biomarkers companies (A, B, C, D and E):

**Type A: ‘Measuring devices and services’**

Companies in the first cluster create value by delivering quality measurements of a specific condition and/or state in the body. The selling point for several of these companies is that their devices and services are more efficient (e.g. cheaper and faster) than current methods. One example is Acorix, which has developed a handheld device called CADScor®System that combines acoustic detection of turbulent arterial flow and myocardial movement to provide a patient-specific CAD score that can tell if a patient needs hospitalisation or not. BrainReader is another example, providing clinicians with a software service called Neuroreader that processes MRI scans in about ten minutes and provides a patient report with measurements of different volumetric data on key segments of the brain.

**Type B: ‘Data generation and monitoring’**

The second cluster comprises companies that generate data in order to monitor a condition, illness, or changes in behaviour over time. The data are typically visualised in tables, graphs, or other representation. Some of the companies also provide users with an opportunity to share their data with a therapist, a caretaker, or other healthcare professional. ICURA, for example, has developed an intelligent home-training system for people in rehabilitation, which consists of sensors that the users strap onto their legs and arms to monitor how they perform different exercises. The collected data are displayed in an app where the users can see, both in real time and historically, how well they perform / performed the exercises. The data can also be shared with a physiotherapist who can use the data to provide

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**Figure 3: Matrix of data sources and key activities**

<table>
<thead>
<tr>
<th>DATA SOURCES</th>
<th>Measuring</th>
<th>Monitoring</th>
<th>Analytics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manually entered</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample/test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provided</td>
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</tbody>
</table>

If we combine these two aspects of the companies’ business models, we get a 4x3 matrix, as seen in Figure 3. That can be used to derive five clusters of digital biomarkers companies (A, B, C, D and E):
feedback on performance and progression. Of the companies in this cluster, two thirds, including ICURA, collect data automatically by one or more sensors. The remaining third relies on manually entered data, sometimes in combination with sensed data. An example of the latter is Monsenso, which offers a solution that supports early intervention and treatment of mental or behavioural disorders, called mHealth. The app collects different health-related data by asking the users to answer various questions about their symptoms and well-being while also sensing the users’ levels of physical activity. Based on these data, the system returns an aggregated score of the persons’ current state to enable the users to learn more about their own illness, but the data are also shared with the users’ clinician and carers with the aim of a better treatment.

**Type C: ‘Data generation, monitoring and personalised decision support’**

The companies in the third cluster resemble those in the second. They generate and collect data to provide an overview of an activity or a process at different stages and/or over time. The difference is that the companies in this cluster also offer some sort of decision-support mechanism based on automated data analysis. Teleskin is one example. It has developed an app called SkinScan where users can take pictures of moles and monitor progression over time. On top of this, Teleskin has developed a machine learning algorithm that analyses the tracked moles and provides feedback to the users and helps them distinguish typical moles from atypical. Another example is Clue that offers an app-based menstruation and health tracker where the users register different details about and related to their period such as duration, flow heaviness, products used, and current mood. Based on an analysis of these data, Clue provides the users with personalised services such as forecasts and reminders about their period, ovulation, fertility, and an analysis of whether the user’s cycle can be considered regular or irregular.

**Type D: ‘Sample collection and analysis’**

The companies in this cluster collect and analyse biological samples for private individuals, exemplified by Qurasense, AthGene, and ExSeed Health. The latter has developed a smartphone compatible device that allows men to test their sperm quality from home, as the sample can be analysed by the device and a smartphone app. Data from the analysis are also sent to a clinician who consults with the user by video. A fourth example is BioWatch that offers a service they call an ‘End-to-end Health Monitoring System’. BioWatch gives athletes and users interested in health issues access to professional laboratory analyses of biological material. They have developed a test kit that contains all the elements needed for a private individual to make a quality sample at home and send it to a laboratory, which then analyses it. BioWatch delivers the results from the test via an app and advises the client on how to improve.

**Type E: ‘Decision support in drug discovery and treatment’**

Companies in the last cluster create value by analysing data provided from other sources. A common denominator is that they all work on developing advanced decision-support systems based on artificial intelligence and machine learning for the healthcare sector. The collaboration between IBM Watson Health and the Rigshospitalet is perhaps one of the best-known examples in Denmark. Another is the Medical Prognosis Institute, which uses machine learning to assist oncologists in identifying the best cancer treatment by correlating data from one patient’s tumour with data from other patients, cell lines, and drugs. A third example is Corti, which has developed an AI–powered decision support system for emergency medical dispatchers that – in real time – identifies important patterns in ongoing conversations and alerts the dispatchers to urgent situations, such as cardiac arrest.
Interviews with the companies – challenges and barriers

Based on the findings from mapping and categorisation, we conducted interviews with ten of the identified companies representing each of the five clusters of companies. The purpose of the interviews was: 1) to reach an understanding of the challenges and barriers to growth that the companies experience; and 2) to use this understanding as input when formulating recommendations for the design of national biomarker infrastructure. The interviews covered topics such as challenges, motivation, and needs. Afterwards, we studied the interview material for recurring themes, which can be summarised under five headings:

CE marking

CE marking of products and services or clinical validation is a field almost half the interviewed companies find challenging. At the time of interview, four companies were either trying to obtain CE mark certification or were conducting trials to obtain clinical validation. They describe the process as difficult to manage, time consuming, and a barrier to taking their products to market. When asked, several of the companies said they would welcome help and guidance on the most efficient way to CE mark medical devices.

Other companies have already made their way over the hurdles. At the time of interview, two had class 1 certification of their products and one company was working on class 2 certification for a medical device. According to four of the companies, CE marking or trials are not relevant; although they have a product or service collecting large amounts of health data, they are not categorised as ‘medical’.

IT security and privacy

IT security and privacy are considered important; two companies told us that they have put a lot of effort into making their product secure as it includes a wearable device. As one of the interviewees put it: “With wearables, we get really close.” Hence, security is important, but in general, most of the companies were confident about their products in this regard. They did not frame it as an issue, and only a couple of interviewees mentioned that they expect to strengthen their security in the near future. In fact, the companies did not express concern about threats like hackers nor other cybercriminals. They were more concerned about issues like GDPR compliance and how they can handle and organise data in ways that secure user privacy without limiting their ability to use the data to develop analytics driven services.

Machine Learning

All the interviewed companies expressed an interest in machine learning, but only a couple have implemented machine-learning-based features into their service. The other companies are familiar with it on a conceptual level and expressed an interest but have not yet begun using it. Most companies expect to exploit machine learning in the future to build services to add to their current offerings.

Partnerships

In a fourth theme, more than half the companies expressed an interest in building strategic partnerships to better utilize the data they collect. Several of the companies have already established partnerships with universities and/or other specialists in the given area; a couple also expressed an interest in hiring an industrial PhD researcher. Other enterprises would like to work together with students from relevant disciplines. One mentioned Medicine and Technology at DTU, while others see great potential in working with the national biobanks and/or Statens Serum Institut (SSI) but need help to establish cooperation. A couple of the companies also see partnerships as a useful way to get through the process of CE marking and/or clinical trials.

User involvement in product development

The final theme concerns user involvement. Here, the companies mentioned a need for dialogue with, and the involvement of, their users and potential users in the continued development of their products and services. A scarcity of time and resources are barriers in this area, as most of the companies are small organisations with many things to do; another challenge to user involvement is physical distance, as most of the companies do not just operate on the Danish market. A couple, typically those with private individuals as customers, had deselected the Danish market at first because people in other countries are more used to paying for health services. This makes it difficult to gather users for traditional user-involvement activities such as workshops, UX tests, and focus groups. In general, however, the companies would like to explore how they can involve users and customers in further development in a well-proven and efficient way. Some of the companies seek feedback on how to display and visualise data. Others are more interested in evaluating the user experience and understanding the specific needs of their different segments of users.
Chapter 5: The potential of active roles for patient associations

Introduction
Driven by the ambition to solve the challenges facing western health care systems, patient involvement has become a central tenet of collaborative projects, thereby adding a new feature to collaboration between the industry, researchers, and patient associations. Hopes are high that patient involvement will find solutions to shortening the path from new discoveries to development and use in clinical practice (Novas, 2006; Callard et al., 2011). The industry has its eye on more sustainable business models (Hoos et al., 2015), while the public authorities see the potential to create a better healthcare system at a lower cost (Coulter 2011): all by means of patient involvement.

Patient involvement is entangled with terminologies of hopes and expectations. This is also apparent in regard to research on biomarkers, which is tied to hopes of earlier and more precise diagnoses, as well as visions of customised treatment that matches the individual patient’s biological and genetic profile. In both areas, the research is in constant, rapid development, yet still in nascent stages, and in both areas, there is a gap between expectations for the future and actual experiences.

Patients have always played a role in biotech and pharma as donors of biological material, as research objects, and as end users. But patient involvement is something else, a matter of involving patients as stakeholders and experts. In this chapter we focus solely on the kind of patient involvement that occurs as part of some kind of organisational development in which patients are involved as representatives (as opposed to the involvement of the individual patient in his own treatment).

Aims
The aim of this chapter is to map the potential and challenges of patient involvement in the development and translation of biomarkers from bench to bedside (Callard & Wykes, 2011).

As actual experiences are scarce, internationally as well as nationally, the chapter addresses the question by focusing on broader experiences and aspirations concerning the positioning of patient associations, and their collaboration with researchers and the biotech / pharmaceutical industries. Particular attention is paid to the political, economic, and socio-ethical dilemmas that arise in this kind of public-private collaboration.

Method
The chapter builds on open-ended interviews with seven patient associations and three researchers, and a follow-up workshop with the patient associations, a review of the pertinent literature on patient involvement and collaboration between patient organisations and industry, and experiences and knowledge presented in a workshop and a debate seminar organized by the project.

This material formed the basis for mapping the type and characteristics of patient organisations and a discussion of the needs, barriers to, and potential means by which patient associations can be enrolled in research on biomarkers and translations from bench to bedside.

Limitations
All patient organisations connected to autoimmune diseases were invited to take part in the project. Most, but not all of them, responded to the invitation. Only one large organisation participated, which means that those interviewed primarily came from small patient organisations with very few or no resources for research and often limited knowledge of biomarkers. While this may, on the one hand, be representative of the landscape of patient organisations, which is indeed characterized by only a few large organisations and a large number of rather small organisations, our choice of sampling strategy has left out the potential and perspectives of large patient organisations occupied with other diseases.
Type and characteristics of patient organisations

The patient associations – What are they?

First and foremost, it is important to recognize that there are fundamental differences in Danish patient associations in regard to size, foundation, and purpose, as well as in their relations to the biotech and pharmaceutical industries.

While some patient associations can best be described as social movements, with large numbers of volunteers gathering around a joint cause, others have been created or initiated by medical scientists who see the potential in strong collaboration between research and the people whom the research is meant to benefit. Some are created to strengthen research and its funding; yet others have been devised on the initiative of pharmaceutical companies who perceive benefit in enabling patients to draw attention to their existence, challenges and, not least, their needs in terms of treatment. Some patient associations are run almost purely on volunteer power, either through permanent members or loose networks who meet through social media. Others have professional secretariats. Many patient associations today work as hybrids with traces of all the features mentioned, but with different emphasis.

In this regard, the formation of Danish patient associations does not differ from that of other countries, such as Ireland (O’Donovan 2007) or Finland (Hemminki et al. 2010). As also emphasised by O’Donovan and Hemminki, it is a simplification to believe that patient associations are social movements that solely speak on behalf of the patient; rather, they represent multiple interests and mandates. Their profiles profoundly impact on the degree of proximity and collaboration with profit-maximizing businesses they can sustain, and are crucial to the role which they see themselves taking in a public-private partnership collaboration on biomarkers.

The role of the patient associations

Traditionally, patient associations have played relatively passive roles in collaborations with developers and scientific researchers. Some have gathered funds and donated them to research, most often guided by an assessment committee consisting of recognized scientific researchers acting as intermediaries. Patients have also participated in research as donors of tissue and blood samples or test subjects but, in these cases, enrolment has rarely been administered through the patient associations. According to those interviewed, tissue and blood donors as well as test subjects are primarily enrolled through the hospitals.

The roles of patient associations are changing, however. Since the first AIDS activists in the 1980s began to affect how research and development is conducted (Epstein 2011), a string of patient associations has taken on other roles in collaboration with developers, businesses, and scientific researchers. Patient activists have in different ways acquired enough biomedical knowledge and language to affect and develop medicine, testing, and licensing (Epstein 2011).

Today, patients and participants from patient associations are frequently invited to workshops related to research or product development to which they are asked to contribute the patient perspective. Patient involvement is currently seen as contributing to more experience-based understandings of problems, treatment forms, and side effects. It can also help highlight unsolved medical needs and assist in the implementation of new research-based insights into clinical practice. According to participants in a debate seminar arranged by the project, patient involvement can thus help secure better solutions. Moreover, several of the seminar participants pointed out that user involvement is an essential democratic imperative; people who are affected by specific research have a right to be heard (see also Elwin et al. 2012, Ives et al. 2012).
In Denmark, the pharmaceutical industry is one of the most active of agents when it comes to involving users in the development of medicine and treatment, yet, when patient organisations receive financial support from the pharmaceutical industry it may raise questions of independence. It puts patients at risk of being exposed as ‘purchased and paid’ and ‘in the pockets of the pharmaceutical industry’. Some thus demand that the question of independence for patients and patient associations should be dealt with in the same way as health professionals who work with the pharmaceutical industry in one way or another. At the project’s debate seminar, participants argued for a publicly facilitated framework for collaboration between patients, patient associations, and industry, as this would help develop the potential inherent in user involvement without the risk of users appearing to be ‘used’.

There is considerable awareness of the risk of being ‘in the pocket of the pharmaceutical industry’ among the interviewed associations. In some cases they express concern about losing autonomy, but they rarely seem aware of the risk of implicitly shifting the patient associations’ focus, workload, and commitment towards the money source. Most patient associations have a limited number of active members and secretarial staff at their service, while many have interests in areas that may not be shared with collaborators in the industry and research worlds, who are more medically and treatment-oriented. These interests include the focus on maintaining an identity as a normal person rather than as a patient, despite chronic illnesses and the desire to meet and share experiences with others in the same boat. There is a risk that such non-profitable goals and stakes suffer when staff and volunteers spend a major part of their time on the agendas that they share with the industry.

In an ideal collaborative arrangement, with all the parties on all sides having economic independence from each other, it would be important to have transparency in the relationship – making public the nature of collaboration, the economic transaction, as well as agreed ethical guidelines for collaboration. It would also be important to have an explicit matching of expectations that takes into account the financial needs of patient associations, which may conflict with the industrial partners’ interests. In all cases, it is necessary for both sponsors and collaborators in development and research to agree on clear ethical guidelines for collaboration and to make these visible for members and the public.

**Relationship to researchers**

As already described, the patient organisations that participated in this project all had a fairly traditional relationship with researchers. Some donate to researchers, especially young researchers, in order to stimulate them to specialize within their specific disease area, thereby supporting the development of new knowledge and treatment within their areas of interest. In other cases they might buy research services with the aim of mapping their needs and creating political awareness.

A new kind of relationship is emerging these days, however. As a response to increased interest in patient involvement on the part of foundations, patient associations are more often invited either to approve or participate as consulting experts in research projects. Having patient organisations on board has become a way to legitimize research and increase the likelihood of funding, although patient organisations that participated in this project are highly aware of the dilemmas inherent in being used this way.

Close collaborations, on the other hand, are rare, although the role of the Danish Rheumatism Association in the establishment of the Danbio biobank is an example of collaboration where the parties become partners; this indicates a move away from the traditional relationship characterised by the principle of maintaining distance, while delegating the research design, set-up, and priorities to the researcher(s) (Rabeharisoa & Callon 2002).

**Relation to private companies**

The patient associations in Denmark, especially the small ones, need a source of income, and the pharmaceutical industry is for many an important source of financing for surveys and campaigns. The interest in collaboration – within limits that legitimate the flow of money from the industry to the patient associations in the eyes of the public – is, therefore, substantial in many associations.

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Needs, barriers and potentials

Patient associations’ competences – needs and potentials

The literature on patient involvement often raises the issue whether patients can have too much biomedical knowledge. The argument goes that patients who participate very actively in research and development may lose a genuine patient focus and grasp of what really matters as a patient. For this reason, and also because patient associations are perceived to have political interests, it is often patients without any relation to patient associations who are recruited to research and development projects. The hope is that they will be ‘pure’ and disinterested. However, as shown by Lehoux et al., no one is free of interest or one-dimensional in terms of position and contribution (Lehoux et al. 2012).

According to an online survey from 2014, the average European citizen has very limited knowledge of developments in medicine today; indeed, 75% had ‘none’ or ‘less than good’ knowledge of medical R&D (Parsons et al. 2015). We do not know if, in general, Danish patients’ knowledge of development and research in biomarkers is any higher, but since it is a smaller field and most research on biomarkers is conducted at a distance from patients, we do not expect so.

There is a fair amount of knowledge in the interviewed patient associations regarding the hopes tied to the development of biomarkers as a potential path to more personalised medicine. There is a keen interest in finding the correct treatment for the individual more swiftly, so that side effects and long periods of treatment without notable improvement are avoided. This is not detailed biomedical knowledge, however, but rather general knowledge that shares the discourse of hope also found in the literature on research in the field.

The degree of knowledge required to become a collaborator in development and research is open to discussion. Some scientific literature stresses the importance of patients’ acquiring competence in biomedical language to enable their participation in the conversation; other sources argue that there is a risk that the genuine patient perspective and experience-based knowledge will recede into the background if patients begin to speak the researchers’ languages (Scheer et al. 2017). One alternative is to facilitate and support translation work between the knowledge forms of patients and researchers respectively, or to involve patients in work processes requiring less detailed biomedical knowledge, such as the problems of early identification and the prioritisation of research needs.

Generally, patients today are rarely involved in the early stages of development. Despite the fact that patients can potentially contribute in all phases, involvement typically takes place in the clinic (Callard et al. 2012). There is a consensus that, in collaborations involving patients, better guidelines and methods are required to make it work and to integrate the different knowledge perspectives in order to establish a meaningful dialogue between patients and researchers. This is a particularly important focus area in terms of R&D in biomarkers, because researchers and developers in the field do not build relationships with patients as part of their ordinary work and, consequently, they risk being ignorant about the perspective of those they are aiming to help. Many years of researching without patient involvement may also leave them with the impression that it is not necessary, and hence they may have limited interest in spending resources on involving patients in their work (Boaz et al. 2014).

Patient associations as fuel to speed up a process?

It may be argued that patients, researchers, developers of biomarkers, and clinicians all have an interest in a common goal: to speed up the process from discovery to market testing and clinical use. But each group also has individual interests that may not be as geared towards the joint process as toward its own incentive for taking part in the journey.

It has been argued that patients are perhaps the partners with the strongest interest in speeding up the process from bench to bedside. There are reports of family members of seriously ill children who have generated breakthroughs in R&D in collaboration with companies by taking a leading organisational role in an otherwise dispersed research field with ineffective collaborative interfaces (Novas 2006). They have also designed and led biomedical research and contributed to the establishment of biobanks (Callard et al. 2011). In Denmark, the Danish Rheumatism Association has been actively involved in the development and establishment of the Danbio biobank, also contributing financially towards it.

These examples demonstrate the potential of offering patient associations a role in the collaborative work of developing and translating biomarkers. However, this is a new playing field, one far from the traditional role of patients as stakeholders with a democratic right to be heard.
The political orientation of patient associations

At the project’s debate seminar on patient involvement in medical research, participants confirmed the dominant discourse that patient involvement is a democratic and ethical imperative. However, ethics have a special significance when it comes to the development of biomarkers. Who can speak on behalf of those who will potentially experience the consequences of new knowledge about biomarkers? For whom can patient organisations speak? Biomarkers and genetic research pose particular challenges for representativeness. Who can represent the citizen or patient and those affected by genetic research when the socio-economic consequences potentially extend far beyond the immediate patient? For example, several researchers have pointed out that biomarkers can provide knowledge that is not only about a tested patient, but also about his family (Svendsen 2003). In other words, research in biomarkers and genetics raises a number of socio-ethical dilemmas related to the knowledge of dispositions and distribution of that knowledge (Callard et al. 2011). (An example is the opposition of civil rights organisations to genetic research into sickle cell anaemia, as they fear the socio-ethical consequences of findings that could potentially link a disease to racial issues.)

We have not identified any clear political positioning in the interviews with the Danish patient organisations. Notions of the possibilities and dangers of collaborating on the development of biomarkers are still unclear to those interviewed. This points to a need for knowledge and capacity-building among all partners in future collaborations with patient organisations.

Future needs

Through interviews with patient associations, it has become apparent that the great leaps expected from patient involvement in medical R&D will not be feasible until the parties involved are much clearer on which, how, and when patient associations are to take an active part in collaboration.

The economic interests of patient associations

In a collaboration in which patient associations and activists are not just contributors, but active players, it becomes clear that businesses and patients do not necessarily share the same interests. Both parties support a swift process from discovery to development and utilisation. But, while businesses have considerable interest in procuring a patent and a pricing scheme that is advantageous to them, patients are likely to have greater interest in sharing knowledge with more scientific researchers. This may contribute to faster development and pricing that will make new tests and medicine attainable and affordable to as many as possible. Thus, patient associations and more loosely organised activists may have an interest in being included as owners of a patent, and as controllers of access to biobanks and biological materials (Novas 2006).

The Danish patient associations we have interviewed do not (yet) exhibit such economic interests, nor have they taken part in the development of biomarkers or genetic research. Their experiences of involvement are limited to voluntarily commenting on redesign, adjustments and utilisation of products. However, several interviewees give accounts of ambivalent emotions when taking part as formally equal participants in a workshop and contributing their knowledge voluntarily, while other participants are being paid to do so.

Some patient organisations employ staff who can participate in research and development and activities related to closer collaboration as part of their job. However, if the small voluntary patient associations are to be involved in time-consuming collaborations, it may be necessary to provide them with financial reimbursement.
Types

It is important to be aware that many different types of, and roles for, patient organisations exist, in Denmark as well as elsewhere. While some can be characterised as grassroot activists, others are professionally organised organisations. Their interest in collaborating in biomarkers research, development, and translations will differ depending on their size, mandate, financial situation, and relationships with researchers.

A way to move forward is by using the points raised in this mapping as a guideline for dialogue and for matching the expectations of research and industry with the patient associations regarding their role and participation in future collaborations.

Barriers and potentials

As shown in this chapter, despite high future expectations of patient involvement, it is still in a nascent state in the field of biomarkers R&D; if patient organisations are to be involved, a number of barriers need to be addressed.

The idea that patient associations consist of volunteer philanthropists who are simply happy if someone wants to research their illness and find a cure must be characterised as naïve. Patient organisations are placed in token and inferior positions if they are primarily perceived as patient representatives with a merely consultative role.

Patient organisations have various potentially conflicting economic and political interests to juggle. They would like researchers to develop tests and treatments for them and wish to contribute to this process, while some associations collect funds which they donate to research. Contemporary patient associations, however, want many things from collaborations. They also want funding and support for their other agendas: money for member care, communication materials, and so on. They are increasingly aware that other actors have commercial and career interest in their knowledge contributions and they would like to have something in return.

It is expensive to develop biomarkers and personal medicine, so it is important to involve patients in the prioritisation of resources: in which areas do they have special interest that could be developed and translated into clinical use? The barrier here is that patient organisations have different interests. Patients can speed up the process of putting research to clinical use by pushing the process, and they can help with prioritisation, so that the most needed tracks of development are taken, but this model requires a completely different role redistribution from what we have in Denmark today. Outside of Denmark, patients have taken leading and facilitating roles in research and development processes, indicating the potential of involving patient organisations. However, this requires a redefinition of roles, and we see no such attempts in Denmark currently.

It seems necessary to equip patient organisations, research, and industry to enter alliances through capacity building. Moreover, in order to avoid a skewing of interest, where researcher and industry participate as paid professionals while representatives / patients from smaller patient organisation without a professional board participate as volunteers, patients should be financially supported in this work.

Patient associations do not wish to be in the pocket of industry or commercial interests more broadly, although many – especially smaller organisations without large public fundraising branches – are dependent on industry contributions. Therefore, any financial transaction in relation to capacity-building should take place through an independent organ.

It is necessary to decide where patient involvement should take place. Ideally patients could be involved in all steps of the development, from identifying medical needs, to research and implementation, which would mean that an actual meeting place is required; this could be both digital and physical in order to organise patient involvement. The clinic is of course an obvious place for the actual research process, but where else would make suitable meeting points for identifying medical needs and implementing biomarkers?

This is a challenge that is especially relevant to both smaller patient organisations and private companies with interests in collaboration, as they do not necessarily have the resources, knowledge, or infrastructure to facilitate collaboration. It is necessary to discuss actively whether and how patient organisations could take part in this, whether contact between patients and companies can be facilitated, and what sort of resources would be required.

Last but not least, patient associations express the wish for independent meeting places in which they can proactively engage in dialogues with researchers and enterprises. Somewhere they may proactively raise their agendas and goals for research and development – as opposed to the situation today where they are mostly reactive responders to ideas and agendas brought forward by either researchers or enterprises.
Throughout our mapping of strengths and barriers within biotech, digital companies, and patient associations, a number of overarching challenges and sources of potential emerge that we need to approach if we are to support growth within the field of biomarkers in the future.

**Stronger biomarkers are a prerequisite for personalised medicine**

Stronger (better validated) biomarkers are needed to implement the concept of personalised medicine. We have identified three challenges in that respect:

- Personal medicine needs to combine the maximum possible biological, chemical, physical, mental, and environmental biomarker data about individuals / groups with many traits in common for the most reliable stratification.
- Biomarker data will be increasingly heterogeneous in type and expression and will need a multi-omics approach and more longitudinal collection of data (‘historical’ data).
- The need for ‘multiplex’ hierarchies of many partially interacting biomarkers at many levels, reflecting differential changes in multi-omics data, sensoric outputs, vision systems, behavioural data, and so on, will require new digital technologies and solutions heavily based upon machine learning and artificial intelligence.

**The process from development to use can be better supported**

Barriers to translations of biomarkers from discovery to validation are well known and are to be found in Denmark as elsewhere (van Gool et al. 2017). Basically, the problem is that, on the one hand, stakeholders at different points in the value chain are deeply dependent on one another, while, on the other, they are organisationally and economically independent entities, who are often not used to collaboration and do not always understand (or prioritise?) the needs of the stakeholders who make up the next link in the chain.

As already described, we have identified two public national organisations that have established expertise central to the biomarker development process: the Danish National Biobank (DNB) to which academic researchers can apply for access to biological samples or data from selected patient groups, and the newly established Copenhagen Centre for Regulatory Sciences (CORS) that aims to create structures, activities, and collaboration models focused on ensuring that drug and biomarker validation is performed to the highest standards, with the most relevant analyses, using the best available materials, and in full compliance with regulatory requirements.

Internationally, we also see organisations working to overcome barriers to biomarker discovery, development, and validation. For instance, HealthRI in the Netherlands, and the European collaboration organ of EATRIS that has gathered members of the scientific community in Europe who are fo-
cused on translational research in order to facilitate easier access to high-end facilities, resources, and expertise; it is also open to collaboration on innovative drug or diagnostic development programmes (there are no Danish members).

Despite these initiatives, however, we have encountered a number of barriers experienced in particular by new companies and SMEs related to access to material, networks, collaboration with researchers and clinicians (without research collaboration, enterprises do not have access to biological material from the biobanks for instance), and regulatory issues that are experienced as rather challenging. Hence, there is a need for stimulating network and knowledge-sharing activities.

**New players can contribute to biomarker development**

In this project we have looked at the process from discovery to clinical use of biomarkers, with a focus on the place and role of two new integrated players in the value chain: players related to digital biomarkers and patient organisations as representatives of the end users.

![Figure 5: New collaboration partners in biomarker discovery, validation, and use.](image-url)
New players mean change of roles for everyone

It seems important to foster an awareness that the new partners in biomarker development do not necessarily want to stay in a position as inferior contributors to the existing field. New partners mean new negotiations of roles, rights, wishes, and forms of collaboration. What are the most important kind of biomarkers to search for? What are the most pressing aims? What is a real biomarker? When does it become something else? Who decides on the endpoint for clinical trial? Who owns data? Who decides to what end data may be used? Who has the right to patents? Who should agree on and set necessary standards for clinical validation of biomarkers? What kind of regulations should apply to new compared to traditional forms of biomarkers? Who decides on pricing and access? And who should share an eventual profit?

So, while new players offer new potential for innovation, at the same time they may challenge existing structures, make new demands on existing regulatory bodies and research infrastructures, and suggest tasks that may best be solved in dialogue between working partners in actual meetings and collaborations. There may be a role for Danish innovation networks in that respect as facilitators.

New kinds of biomarkers are on the way

Digital companies collect large pools of behavioural data that may be used to suggest new kinds of biomarkers predicting the status of health as well as treatment needs. Thus, some of the answers once sought via biological biomarkers, may be found in the future through detection of patterns in digital or behavioural biomarkers.

Within R&D of personalised medicine there is an increased awareness that a single biomarker will seldom be sufficient to predict the actual treatment needs [doses as well as type of medicine] of the individual, which are also influenced by factors such as lifestyle choices. Hence, there seems to be a great potential in analytics of combinations of biological and behavioural data. Many experts envision a future of ongoing data collection via multiple sources, with medical breakthroughs occurring as a result of such endeavours (Stanford Medicine 2017 Health Trends Report). Along the same lines, the Danish public-private partnership project, HealthD360, is just starting up. The goal of HealthD360 is to discover how to combine data from wearables, for example, and health data from patients’ electronic medical records; it will be interesting to follow that work and evaluate how it can contribute to developments within biomarker R&D.
Hence, expectations are high, but the research field is in a nascent stage and there are a large number of technical, ethical, and juridical questions that remain to be solved. In this report, we have investigated the state and needs of Danish digital companies. It is clear that there are many start-ups and small companies in the field that could use external expertise – in particular tech capabilities – to help them scale up and realize their commercial potential. Many companies offer services that collect data about a condition over time and have now become administrators of large amounts of data that potentially could be used for different kinds of analysis, such as pattern recognition and perhaps identification of new biomarkers.

In short, if the Danish digital companies are to find a toehold in the growing digital biomarker market, it will demand capacity building, an awareness of the kind of knowledge they lack, and networking opportunities – much the same as within the life-science / biotech fields, but focused on the special needs of these rather small, youthful enterprises.

### New kind of end users change the market

Companies working with the ‘Internet of things’ relate to end users in different ways than were common in the development and use of traditional biomarkers. To them, end users are not passive contributors of blood or tissue, but active collectors of data who may – or may not – wish to share their data with their clinicians and with researchers who want to study data patterns. They are often direct customers in search of the means to optimise their health and wellbeing. In many cases these customers are very conscious of the use to which their health data may be put, and select companies based on the transparency they offer in connection with data use. As such, not only the roles and positions of the different stakeholders but also the market is changing. The end user is no longer the publicly funded health care system (alone) but as much a private market with private customers.

This trend may indeed change the market for biomarker-based products, meaning it is important to keep up to date on the development and support needs within this fast growing field. This way it may be possible to foster synergy between development in traditional markets close to the established health care system, and the new markets targeting private customers.

### New markets are international

Last but not least, an important point highlighted by all the interviewed stakeholders is that the new markets are international. Danish citizens and the Danish health care system may not even be seen as end users – markets in other countries may appear more attractive to Danish companies.

Accordingly, Danish companies need knowledge of international regulations, including those outside of the EU, rules of reimbursement, international markets, and possibly international collaboration partners among enterprises, researchers, and patient organisations, who may offer culture-specific knowledge on end users’ needs and perspectives in the targeted market.

Likewise the stakeholders may seek partners for the provision of data and tissue, and research and validation internationally; hence, support for collaboration, partnering, and matchmaking might have an important role in Danish biomarker business growth, both in terms of new business activities for existing companies, and for new start-ups supplying those needs presently outsourced to international players.
Chapter 7: Recommendations

To realise the above-mentioned potential and overcome the challenges described, there is a salient need for long-term investments in capacity building, bridging, network support, and infrastructure. As such, our recommendations are in alignment with the OECD’s recommendations from 2011 as described in ‘Policy Issues for the Development and Use of Biomarkers in Health’ (OECD 2011) as well as the Danish Research Strategy FORSK2025.

Our dialogues with stakeholders throughout the project have given rise to concretizations of such needs for capacity building, internationalisation, and strengthened structures for long-term relations between research institutions, enterprises and – a new initiative – patients represented by patient organisations.

In the following section we present ideas for:
- Capacity building and bridging activities
- Infrastructural activities and stronger long-term ties across sectors and national boundaries

Capacity building and bridging activities

A number of common needs appear among pharma, biotech, and digital companies. Particularly important amongst these requirements are:
- Access to biological material and digital data in which to search for biomarkers
- Consensus agreement on standards and quality of data
- Consensus agreement on standards for reporting and sharing data that makes it possible to make integrative analysis
- Consensus agreement on validation of biomarkers
- Knowledge about trials, CE marking, and other regulatory issues
- Places to meet
- Bridging between enterprises with digital competence and actors within the established health care system
- Bridging between life science and digital science
- ‘Syndicated power’ in dialogues with politicians, authorities, hospitals, and biobanks (access to tissues and data as well as regulatory issues) where a joint biomarker voice would be much stronger than approaches from individual companies or stakeholders that would often be considered too specific or associated with potential conflict of interest issues
- High data security and clear guidelines for sharing of data

Patient associations may be important stakeholders, especially when it comes to data sharing, as representatives with a democratic right to take part in decision making about what data may be used for and how.

There is a mutual interest for all actors in speeding up the process from early research to development of validated biomarkers (both traditional and digital). In order to push this development, several points need to be addressed and clarified. Among these are the involvement of patients, not only as stakeholders but also as potential partners. In order to pave the way, we recommend capacity building that specifically targets patient or user involvement. As part of this there is a need to create:
- Greater awareness of patients in marketing relations and research relations – and the pitfalls and potentials in those kinds of alliances
- Capacity-building among all partners by an independent organ – with a focus on how to harvest the very different perspectives and competence of companies, patients, and researchers
- Fundamental knowledge and understanding of the support needs of patient organisations and the advantages of incorporating patient perspectives
- Knowledge sharing with examples of good cases of collaboration between industry, academia; and patients
- A meeting platform
- Code of conduct to guide partnerships and collaborations
Strengthening innovation infrastructures to foster growth

Infrastructures that foster and support long-term collaboration and support of innovation and growth areas are pointed out as crucial to national as well as European strategies for research and innovation. In addition, the stakeholders that engaged in dialogues with us have underlined the importance of neutral, economically independent meeting places for the exchange of knowledge and to initiate closer collaborations.

The task

The stakeholders involved in this project had a number of wishes with regard to infrastructure development. Among the infrastructural tasks and functions that stakeholders find important are:

- A platform to facilitate collaboration between the industry, researchers, and patient organisations
- A multidisciplinary support function for biomarker development and validation projects
- Guidance from independent clinical experts
- Knowledge sharing between all collaborators and stakeholders
- Match-making
- A platform from which to address the most important generic challenges across companies working with biomarkers including: regulatory requirements (labelling, etc.), access to samples, materials (through biobanks) and patents
- Help in applying for funding for public biomarker development
- Facilitation of a national strategy in the field
- Facilitation of improved guidelines for the use of biomarkers in clinical testing
- The generation of new projects that foster concrete discovery and validation
- Establishment of ethical guidelines for cooperation between patient organisations, researchers, and private businesses
- Empowerment of patients to render them active contributors in defining and prioritizing biomarker research efforts

Figure 6: Overview of a national Danish infrastructure

Stakeholders and partners – people and organisations

- Researchers
- Clinicians
- Patient organisations
- Public and private organisations, as e.g. biobanks
- Clusters, national and international
- GTS Institutes
- Politicians
- Regulatory bodies
- Independent clinical experts

Economically independent management

Funding

Value creating outcomes

- Matchmaking
- Knowledge sharing
- Outreach
- Lobbying
- Access to data
- Clinical trials
- Regulatory and IPR guidance
- Facilitation of innovation and entrepreneurship
In addition, patient associations ask for independent meeting places in which they are not reactive contributors to the agendas of other stakeholders, but proactive partners of collaboration catalysing new ideas and new agendas for research and translations. To our knowledge, there are no infrastructures in Denmark today that create such space for patient organisations, but taking the example from the Netherlands, UK, and EUPATI-DK, we may get inspiration to create such facilities and make it an integral part of a national biomarker infrastructure (Spindler & Lima forthcoming).

Our ongoing dialogues with stakeholders point to the importance of thinking internationally. We have in Europe a number of research infrastructures, among these BMRIIt and EATRIS, which could be important affiliates. Danish infrastructure work should collaborate closely with these international organisations if we are to meet the needs of Danish innovative enterprises.

In short, the Danish innovation infrastructure needs to be cross-sectoral, include the civil sector, and collaborate closely with international organisations, with a view to international research collaborations, international regulations, and international end users.

These needs are visualised in Figure 6.
In conclusion, we believe that Denmark has a unique and special position from which to conduct the efficient exploitation of the potential of biomarkers both from an industry point of view and as an important tool in the healthcare system to improve treatment outcomes. Denmark has already launched a number of initiatives [e.g. the National Genome Centre, the Danish National Biobank, and the Danish Cancer Comprehensive Centre] that focus on the implementation of personalised medicine or provide essential resources, and would integrate well on a number of levels into a more dedicated biomarker development and validation infrastructure.

The total biomarker market has an estimated global CAGR of 11-12% over the next 5 years, and for diagnostic applications alone the w/w CAGR is estimated as high as 16%. In this field we have identified a portfolio of Danish growth companies, particularly in the diagnostics, bioinformatics, and digital health segments. Through development of innovative technologies brought to the market, they have already shown high growth rates and expect substantially increased five-year growth rates, both in number of employees and turnover – provided that a range of challenges can be overcome and barriers removed at an aggregated level.

We have identified needs for sustaining and developing research and innovation infrastructures for biomarker discovery, development, validation and translation to the clinic. Such infrastructures should allow open and transparent relationship building through matchmaking and knowledge sharing between stakeholders and professional disciplines. Facilitated access to core infrastructures such as biobanks, high-cost equipment and to clinical trials should also be supported. We see strong potentials and value in improved integration between:

- The life science and digital disciplines
- The ICT/digitalisation and patient involvement dimensions
- Patient involvement, research, and the biotech/life science industry

Current supportive infrastructures appear fragmented when it comes to biomarker development and clinical translation. Thus, efforts to significantly improve integration between existing structures, e.g. biobanks and clinical trials, as service provisions to researchers and companies are warranted. There is a need to improve services in regulatory advice and IPR issues concerning biomarker development.

As an outcome of this project, actions in 2019 and 2020 will be taken by the innovation network Biopeople to sustain network activities and build new services in the fields of matchmaking, knowledge sharing etc. between stakeholder groups.

The project identifies a need for a more efficient coordination between existing infrastructures to deliver transparent and flexible services for researchers and companies, including SME’s developing and validating new biomarkers.

The project also identifies a clear need for company-specific guidance through the biomarker development process, including guidance on validation, clinical translation and market access aspects. Further work is needed to develop specifications of an infrastructure that can deliver customised services to companies. Further work is also needed to define a business / funding model for a function that can deliver such services.

We believe that such investment in biomarkers’ infrastructures will lead to significant growth in value creation for the Danish society at large.

We expect that the growth in value creation will take place across the whole field, consisting of intellectual, industrial, economic, and societal dimensions:

- New research results and scientific hypotheses will lead to new discoveries, technologies, analytical methods, and integrated biomarker panels (intellectual value).
- Innovation and business creation driven by both entrepreneurship and intrapreneurship activities (intellectual and economic value).
- Industrial growth and increased exports (industrial and economic value).
- Overall economic growth, job creation, and improved quality of life (societal value)
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- Tomasz Wojdacz, MethylDetect
- Ulf Christensen, PentaBase

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