Programme 4D is a Swedish collaboration between Karolinska Institutet and Stockholms läns landsting / Stockholm County Council

Research Appendix

There is an extensive collaboration between healthcare and medical research in the project groups of Programme 4D. The sharing of information enabled by the programme also improves options for transferring information from healthcare to research, thereby promoting new knowledge. This can be achieved, for example, by using information from healthcare data, quality registers and biobank samples, and patients' health self-assessments. This knowledge will be applied from research to the healthcare system in the form of new or improved treatment, prevention or diagnostics.

This appendix contains a short description of the ongoing research that is coupled to the projects within Programme 4D.

4D Arthritis

Background

Chronic non-curable inflammatory joint diseases affect more 1% of the general population. For Rheumatoid Arthritis, the most common of these diseases, the life-time risk is around 1 in 30 individuals, and twice as high in females as in males. Besides reduced prospects for healthy living and active ageing for patients diagnosed with these conditions, the societal dimension of inflammatory arthritis includes substantial costs in terms sick-leave and disability pension and for healthcare services and treatment. For instance, "Biological drugs" are efficacious in many but far from all patients with chronic inflammatory diseases such as Rheumatoid Arthritis, but currently account for over 5% of the entire drug expenditure in countries such as Sweden. Yet, the societal costs related to reduced workability in this population are even higher.

Research Agenda

For Rheumatoid Arthritis and many other chronic inflammatory diseases the unmet medical needs, and hence our research agenda, can broadly be summarised as i) identification of individuals at high risk, including targeted interventions among them ("personalized prevention"), ii) early identification of individuals with new onset disease, and iii) an individualized approach to treatment and monitoring of the disease ("personalized treatment"). To address these needs, we need to find ways to identify the various subsets of the disease, to learn about the etiologies and molecular pathogenesis of these subsets, and to help developing and evaluating prevention and therapies that specifically address modifiable risk factors (life style) as well as molecular pathways towards disease. Finally, we need to measure treatment response, treatment side effects on individual as well as societal level (figure below).

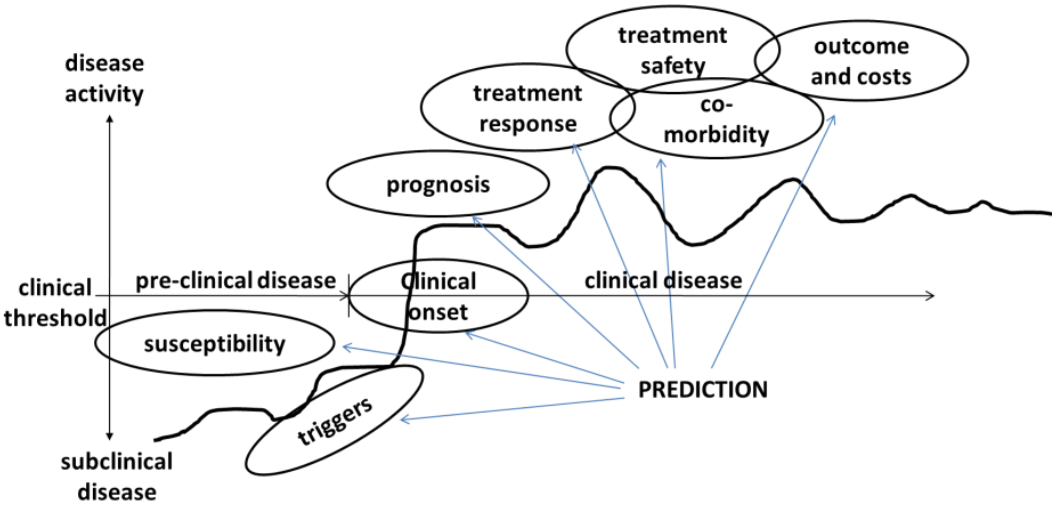

Figure 1. The needs for improved predictions in order to achieve targeted prevention and personalized treatment in RA and other chronic inflammatory diseases

Key to success of prevention and treatment is the contribution of the patient her/himself both in terms of contributing data about her/his disease, and in terms of access to information that enables the individual/patient to take maximal control of her/his disease.

Arthritis research in the 4D program aims to use a unique opportunity now provided, to combine detailed information directly from patients, with clinical, molecular and epidemiological studies aimed at developing and evaluating preventive as well as therapeutic approaches to RA. Informatics is also a key component of our work, to ensure novel solution for capture of information, to bring together information from the different sources both for research and for clinical care. The combination of qualified science in all these areas, with the addition of unique new instruments for patient participation presently provides us with a very strong international edge in several fields of arthritis research. This edge enables us to leverage the grants for 4D with major additional funding from international funding agencies as well as from international companies, thus contributing to better care as well as a better environment for research and industrial development in the Stockholm area.

Below follows some examples of progress made during the year, where the 4D program has contributed to the results:

a) **Development and use of new tools for patient participation in care and research:** A major efforts has been made to create new systems for communication between patients, care and research. A specific electronic tool (ontilederna.nu) has been established as a pilot for individuals with symptoms of suspected arthritis to self-evaluate and to use decision support based systems for contacts with primary and specialist care.

b) **Development of new biobanking programs integrated with electronic records and quality registers:** A new systems for integrating biobanking with electronic records and quality of care registers as well as with clinical trials programs has been developed. The system is currently subject to piloting and evaluation in the arthritis program, and will be a major tool for all specialties in obtaining biobanked material from routine care (http://srq.nu/srqny/wp-content/uploads/2014/04/SRQ_Biobank_patientinformation.pdf).

c) **Use of these tools to develop programs for earlier diagnosis, prevention and earlier therapy:** The systems for communication with and obtaining information from patients, in combination with molecular/genetic data, permit us to develop "personalized" programs for prevention and treatment. Such programs are currently being developed and evaluated, and will take molecular knowledge (biomarkers, genetics) (1-4), new clinical techniques (including ultrasound) (5) as well as life style (6-8) into account in advising patients and care givers about optimal ways for preventions and treatments. A clinical trial ongoing in all Nordic countries, coordinated from Karolinska (called NORDSTAR), comparing 4 registered treatment options at arthritis diagnosis, also aims at finding predictors of treatment response. The ultimate goal of all these initiatives is an individualized treatment strategy for RA.

d) **Development of programs for evaluation of care from the perspective of the patient, the care giver and the society (an aspect of value-based care and a preparation for a new system for quantifying relevant outcomes):** We use the unique Swedish opportunities for outcome research to evaluate effects of different preventive and therapeutic program concerning effects for the

individual (quality of life, including work capacity, disease comorbidity and treatment safety) (9, 10), for care givers (effects on clinically measurable outcomes) (11) and for society (effects on disease, compared with costs for society).

e) **International collaborations:** The 4D program has helped in establishing and strengthening several international collaborations, including the securing of a new big IMI program for drug development (ULTRA, managed from KI), as well as the further development of to other IMI programs (BTCure, KI EU coordinator http://btcure.eu/) and AbiRisk http://www.abirisk.eu/.) A number of additional international bilateral collaborations have been developed and strengthened.

f) **Collaborative programs with industry (pharmaceutical, diagnostic and informatics companies):** Several industrial contracts have been established (PhaDia/Thermo, Janssen, AstraZeneca). The diagnostic program has resulted in a new diagnostic system for autoantibody diagnostics in RA. The other programs are presently focused on biomarker development.

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4D Breast cancer

Background

During the period 1980-2011, the incidence of breast cancer increased nearly three-fold on the global level. In 2012, nearly 1.7 million women were diagnosed with breast cancer (Ferlay et al. 2015; Forouzanfar et al. 2011). Sweden has seen a similar trend since 1960. A total of 9,123 breast cancer diagnoses were reported in 2013 in Sweden, 1,667 of them in Stockholm County (Cancerstatistik 1970–2013). Sweden's outstanding breast cancer survival rates are based on the high standard of palliative care, a national mammography screening programme and frequent use of the latest adjuvant therapeutic regimens (De Angelis et al. 2014).

The 4D Breast Cancer Programme has multiple aims, with the overarching goal of reducing incidence and mortality of breast cancer. The proposed programme will significantly reduce the burden of breast cancer through a personalised medicine approach that takes into account individuals' risk and prognosis of breast cancer.

Integrated Practice Units

Breast Cancer Centres are currently undergoing further development at three large hospitals (Karolinska University Hospital, Capio S:t Göran Hospital and Stockholm South General Hospital) in Stockholm. The goal is to integrate research and development activities with clinical practice. The value-based healthcare model suggests that, in order to maximise patient value, care should be delivered in integrated care units, also referred to as integrated practice units (IPUs). These units comprise co-located, multidisciplinary teams that provide the full cycle of care for a breast cancer patient. This includes inpatient, outpatient and rehabilitative care as well as patient education and follow-up. The unit is designed to reduce multiple fragmented medical appointments and tests by consolidating these at one clinic focused on one condition. The unit's integrated process will create the infrastructures needed to conduct unique clinical-oriented research. The specific aims are:

- To give all women visiting the units the opportunity to contribute to clinical studies
- To create the integrated health care process needed to enable patients to participate in randomised clinical trials
- To expand breast cancer care and research to include primary prevention and early detection
- To create a well-annotated biobank of blood, primary tissue and metastases
- To link the biobank laboratory information system (LIMS) to the regional quality register of breast cancer patients
- To develop and evaluate breast cancer surgery, oncoplastic surgery, primary/secondary reconstruction and quality of life
- To evaluate how sentinel node biopsy influences staging of the axilla, arm morbidity and survival
- To evaluate hereditary aspects of breast cancer
- To identify biomarkers that predict therapy response and prognosis

- Participate in developing new anti-cancer drugs and therapy concepts aiming at controlling systemic disease aiming at increased cure at best palliation at relapse
- Tailor the use of the interfoliated local- and locoregional radiotherapy
- To include research focusing on care, psychosocial support, rehabilitation and quality of life for breast cancer survivors

Research agenda

1. The dynamics of setting up the IPUs

To enable cross-case comparison, each of the three units will be treated separately. Questions to be answered include: How are processes and mechanisms being set up in the new breast cancer IPUs? How is the choice of process affected by the clinical unit's specific conditions? What are the main problems involved in implementing the processes and mechanisms? How successful is the chosen approach in each case?

2. Using experience-based co-design to develop patient reported outcome measures (PROM) for implementation in the Swedish national breast cancer quality register

The aim of this project is to develop a structured method and a technological solution for assessment of the relevant PROM to be implemented in the Swedish national breast cancer quality register. The project has produced a PROM questionnaire that has been tested in the target population. The PROM questionnaire is ready for widespread national implementation in the quality register. In 2014, data collection was completed and analysed for the three-stage project and a scientific manuscript was submitted for publication.

The quality register is in use, with high compliance levels for surgical parameters. Development is required, however, with regard to reconstructive surgery and oncology. In order for the oncology parameters to be useful in clinical practice, registration needs to be expanded, access to data on the patient level needs to be immediate, and compliance needs to be improved.

3. Identification of the individual risk of breast cancer

There are several models that predict the individual risk of developing breast cancer. Most are based on a compilation of lifestyle factors and family and reproductive history. We will use data from a large Swedish cohort (n ≈ 33,000 participants) generated at the South General Hospital [karmastudy.org] to create a prediction model that includes genetic makeup and mammographic density (Michailidou et al. 2013; Darabi et al. 2012). Such a model will be used for individualised breast cancer prevention and screening. Two newly accepted Horizon 2020 grants (BRIDGES, B-CAST) support this aim.

Our goal is to provide the option of having the individual risk of breast cancer assessed at the first screening. Women at high risk of breast cancer will be offered opportunities to influence their risk level. The first step will be lifestyle counselling covering factors such as weight loss, increased physical activity, assistance with supervised physical exercise, and reduced alcohol intake. The lifestyle improvement support system will include innovative interactive e-health solutions. This part of the project is conducted in collaboration with the Universities of Utrecht (Carla van Gils) and Copenhagen (Elsebeth Lynge), and an application to the European Commission is being prepared. The aim is to offer women at very high risk of breast cancer risk-reducing medications at a dose that

minimises side effects without sacrificing preventive effects. The study started in March 2015. The Swedish Research Council (Vetenskapsrådet) recently awarded a grant to the subproject that is testing risk-reducing medications.

4. Risk-based breast cancer screening

Today's breast cancer screening programmes (offered in most European countries from 50 years of age) are based on health economic studies from more than 35 years ago. Typically, age is the only discriminator used to determine the need for breast cancer screening. Today's screening programme therefore fails to pick up other known breast cancer risk factors such as lifestyle, genetics and breast density (Hall & Easton 2013). The omission of breast density is particularly troublesome, as quite a number of women screened have breasts with high density. A comprehensive solution for automatically measuring mammographic density was initiated at the South General Hospital in December 2014 in collaboration with the image analysis company Volpara.

In 2015 we will move from age-based to risk-based screening for a subset of women visiting the screening units in Stockholm. The aim is to use alternative techniques ("abbreviated" MRI) for women with breasts of high mammographic density. An application to the Stockholm County Council (ALF) was recently submitted to cover the cost of this project.

5. The Oncogenetic Clinic

Approximately 10-15% of all breast cancer is deemed hereditary. Demands for genetic counselling and individualised risk assessments are increasing among patients and the community at large. Previously, mutation screening only targeted alterations in BRCA1 and BRCA2. However, breast cancer can also be a part of cancer syndromes involving other genes such as ATM, CHEK2, PTEN and TP53. Using modern molecular technologies such as sequencing, new potential cancer genes are continuously identified and evaluated.

Studies on hereditary breast cancer currently underway at the Karolinska Institute involve next generation sequencing to identify novel breast cancer-associated genes. The genotype/phenotype aspects of germline mutations in the tumour suppressor gene TP53 are also being studied, as well as the effect of TP53-targeted therapy in these families. Clinical trials evaluating targeted therapy with PARP inhibitors in patients with BRCA-related breast cancer are also running, as are studies on the psychosocial aspects of hereditary cancer syndromes as a key factor in familial cancer.

6. Breast cancer surgery

The sentinel node in breast cancer is the first node that drains the tumour, and removal of only the sentinel node is a technique that has replaced axillary clearance in node negative cases (Andersson et al. 2012). Thorough evaluation has not been conducted in terms of whether a full axillary resection is needed in sentinel node positive cases. Surgeons in Stockholm are participating in a large Scandinavian randomised multi-centre study (SenoMAC; 3,700 cases) focused on evaluating the need for axillary resection in sentinel node positive cases. Doctor de Boniface is the principal investigator. The role of sentinel node resection in highly malignant breast cancer cases treated with neoadjuvant therapy is being tested in a national multi-centre study headed by Professor Frisell.

Oncoplastic surgery is a combination of breast cancer surgery and plastic surgery. New techniques need to be evaluated in trials and correlated to oncological safety, and several studies are underway

(Eriksen et al. 2011). Primary reconstruction with Acellular Dermal Matrix appears to produce a better cosmetic outcome and is being tested in a large national randomised trial in Stockholm. Another study, conducted in Stockholm, is examining the risk of recurrence in breast cancer patients that undergo secondary reconstruction several years after primary surgery.

7. Breast cancer oncology

Primary breast cancer – neoadjuvant and adjuvant therapy concepts

Pre- or post-operative adjuvant therapy of micrometastatic disease are critical elements in the management of breast cancer patients. The previous generation of adjuvant chemotherapy followed by a five-year course of Tamoxifen reduces the breast cancer mortality rate by 50% at fifteen years of follow-up (EBCTCG 2005, 2011, 2012). Post-operative radiotherapy also improves breast cancer and overall survival rates, when combined with surgery and systemic therapies (EBCTCG 2014). The latter survival rate improvement should be interpreted with some caution, however, since we do not have data on the best and most modern adjuvant therapies. While adjuvant systemic therapy and radiotherapy have positive effects, they also have well-documented short-term side effects and, in some cases, also very severe long-term consequences. Primary systemic breast cancer therapy is currently aimed at controlling the local-regional disease as well as the micrometastatic systemic disease. Chemotherapies, with different drug selections and schedules and targeted agents (primarily anti-HER2 agents), the latter of course including endocrine agent, is the armamentarium. This is a research-intensive area but we need to be better in avoiding both over- and under treatment.

Several randomised studies run in the ‘90s compared identical chemotherapy regimens before and after surgery; no statistically significant differences in survival rates were recorded. In a recent randomised study, however, the option was offered to non-responders to switch or prolong therapy, and an improvement in disease-free survival was recorded (von Minckwitz et al. 2013). These data indicate that the in situ monitoring of therapy effect during neoadjuvant therapy is a potential advantage in comparison with adjuvant therapy. More recently, an FDA-initiated meta-analysis of nearly 13,000 patients showed that patients achieving pathological complete remission (pCR) had a statistically and clinically meaningful improvement in event-free and overall survival (Cortazar et al.). The frequency of pCR with modern therapies, in particular for patients with HER2-positive disease, is in the order of 50-60% (de Azambuja et al. 2014, Gianni et al. 2012, Schneeweiss et al. 2013).The correlation between pCR and outcome remains controversial and has been criticised in another meta-analysis (Beruttiet al. 2014).

The use of neoadjuvant therapy will likely increase due to its potential to allow for switches of therapy. Based on this concept, a prospective and randomised study has been launched for the HER2-positive group, and further studies are planned for the luminal A-, luminal B- and the triple negative subgroup of patients. To some extent, the division of breast cancer into biologically distinct entities can be performed by immunohistochemistry, but it is clearly best performed by modern gene expression profiling or RNA-based sequencing.

Studies on better prognostication and therapy prediction are all aimed at tailoring management for the individual patient with a focus on avoiding over- and under-treatment, which is a real problem with today’s management.

Metastatic disease

Despite modern management, some 20% of breast cancer patients will recur. Triple negative breast and HER2-positive cancers typically have recurrences within the first few years of follow-up, while luminal A-cancers in particular may have recurrences at a much longer follow-up (although with present adjuvant standards most of these patients have recurrences within 10 years). At time of relapse, the metastatic lesions may "change characteristics", likely due to therapy-induced clonal selection by the neoadjuvant/adjuvant therapies used (Lindström et al. 2012).

Fifteen to thirty per cent of breast cancer patients seem to lose the presence of ER expression in their recurrent cancers (Lindström et al. 2012; Karlsson et al).Two recent publications have demonstrated that mutations occur in metastatic breast cancer in the oestrogen receptor domain, which partly explains the lack of endocrine response in patients with initially ER-positive breast cancers. In general, the clonal selection for HER2-positive disease is considered to be smaller. Finally, a few percent of the patients have gain of ER- or HER2-positivity in their tumour relapses, which will quite dramatically alter the therapy options in the recurrent setting. New cancer drugs, including "targeted agents", are frequently developed in the metastatic setting and later studied in the neoadjuvant and adjuvant setting.

Research strategies for primary and advanced breast cancer

Based on these brief descriptions, it is clearly important to characterise in detail the biological features in both primary and recurrent breast cancer, using the most modern standards for biological characterisation (RNA-based sequencing and gene expression profiling) and the best available imaging strategies (MRI-/PET camera studies), ideally with tracers with drug- or tumour-targeting capacities.

Accordingly, the research strategies described above must be applied and developed in clinical studies at the departments that are involved in developing new drugs and new therapy concepts, including modern dosing strategies. Major focus should therefore also be directed at understanding variability in toxicity and its potential relationship to outcome, through analysis of the single nucleotide polymorphisms (SNPs) for drug activating and metabolising enzymes.

8. Prognosticators, therapy predictors, ClinSeq

In order to avoid under- or over-treatment, it is highly important that the markers that are used and established have analytical validity, clinical validity and clinical utility. A fairly well-established set of markers are currently used for breast cancer management (Er, Pr, HER2 and Ki-67, a proliferation marker), but do not provide a complete picture. Consequently, under- or over-treatment is not infrequent in primary breast cancer management. There is an urgent need to fine-tune and develop better markers for prognostication and therapy prediction. Several gene expression signatures have been described and validated on other data sets, and prospective and randomised studies are ongoing in the international arena. A more realistic future approach is to identify prognosticators and therapy predictors and validate them on clinical studies/population-based cohorts that have already been run, thereby avoiding a marked delay in their introduction for patient management.

We are currently conducting a pilot project with StratCan (ki.se/stratcan), theClinSeq project, where this type of molecular characterisation is run on primary breast cancers. A further study is needed to confirm the initial results. In short, this type of platform will provide an improved prognostication.

This method clearly adds value by analysing multiple additional genes of potential importance as being “targetable” and “drugable” genes, based on their mutational status.

9. Care Science

Current ongoing research on supportive care in breast cancer is focused on randomised intervention studies to support women with self-care to alleviate symptoms during treatment. The relationship between symptoms, haematological toxicity and genetic factors remains unknown, and raises questions concerning the value of studying symptom clusters in conjunction with genetic profiling to improve symptom distress and health status for women with early stage breast cancer.

Different types of interventions (e.g., physical exercise during chemotherapy and post-treatment using innovative e-health solutions) are implemented clinically and evaluated. The hypothesis is that an interactive mobile phone/tablet for reporting symptoms, supportive self-care advice and instant access to health care professionals promotes safe and participatory care for patients with long-term conditions and thereby improves clinical management and health economics.

The lack of evidence from randomised trials concerning optimal training to improve symptom management during chemotherapy for women with breast cancer prompted an intervention study aimed at investigating how different training interventions affect physical capacity and physical and psychological well-being. The primary outcomes are symptoms and quality of life; the secondary outcomes are the impact of biopsies and blood analyses on muscle and blood. Patient inclusion and data collection are currently underway.

9. Biobanking

The aim of the Stockholm Medical Biobank is to be a regional biorepository of health care and research samples. All processes will be integrated with the health care system using electronic sample tracking with 2D barcodes, comprehensive logistics, collection of electronic informed consents, and linkage to clinical data ensuring patient integrity. This guarantees rapid processing of samples and documentation of quality. Stockholm Medical Biobank uses the 4D projects to establish high quality biobanking processes. These processes will be used as models for the collection of other research or health care samples. Biobanking includes sample collection, transportation, pre-analytical handling and short- or long-term storage.

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4D Diabetes type 2

Background

The prevalence of type 2 diabetes is increasing worldwide and especially in low-income countries (International Diabetes Federation 2013). In Sweden the current prevalence is estimated to about 5 % (International Diabetes Federation 2013, Andersson T et al. 2014, Ringborg A et al. 2008). Undiagnosed type 2 diabetes is common, mainly due to the absence of symptoms at mild to moderately elevated levels of blood glucose. About one in three people with type 2 diabetes are probably undiagnosed (Ringborg A et al. 2008, Carlsson S et al. 2007). In addition there is an unknown prevalence of prediabetes (IFG, impaired fasting glucose or IGT, impaired glucose tolerance) (Nathan DM et al. 2007). Prediabetes has however a higher prevalence than manifest type 2 diabetes (International Diabetes Federation 2013) and people with prediabetes have been shown to be at a high risk of developing diabetes (at least 40% within a 10-year-period), if not prevented (Nathan DM et al. 2007). Several studies have shown that prevention of diabetes from prediabetes is possible with life style and/or pharmacological intervention (Gillies CL et al. 2007).

The risk of developing type 2 diabetes is partly due to genetic background (Herder C et al. 2011), partly to factors in lifestyle or environment affecting insulin sensitivity and pancreatic beta-cell function (insulin producing capacity) (Östenson C-G 2001). Important risk factors causing impaired insulin sensitivity are overweight and obesity, ageing, physical inactivity, tobacco use and psychosocial stress (Hamman RF 1992, Hilding A et al. 2006, Eriksson AK et al. 2008, Cullmann M et al. 2012, Deleskog A et al. 2012, Östenson C-G et al. 2012, Eriksson AK et al. 2013). Increased knowledge about the interplay between genetics and lifestyle / environmental factors (epigenetics) may contribute to the understanding of the origin of the disease, the development of complications and the optimization of prevention and treatment. Type 2 diabetes is a chronic disease that often leads to costly consequences for both the person and for society (Ariza MA et al. 2010). In Stockholm County Council (SLL) about 10 % of the healthcare budget is allocated to diabetes-related costs (Personal communication 2014), mainly to the care of complications such as cardiovascular diseases, kidney failure, the “diabetic foot” and retinal impairment.

Research Agenda

Early detection and possibly prevention of disease is thus a major aim of the 4D type 2 diabetes project. It is common that a person with prediabetes or early diabetes has no, or only minor, symptoms but is at risk of developing complications. These are macrovascular, such as ischemic heart disease, peripheral artery disease and stroke, and microvascular, affecting the retina, kidney function and peripheral nerves. A high proportion of those today diagnosed with diabetes and prediabetes have non-European background (Wändell PE et al. 1997, Wändell PE et al. 2010). Other risk groups are people with mental illness (Ösby U et al. 2014) or poor dental health (Sultan A et al. 2014). There is no evidence that supports screening of an entire population, while screening in high-risk groups is probably beneficial (Gillies CL et al. 2008).

There are large variations in health outcomes for people with diabetes between the more than 200 primary care units in the SLL. It can only to a small proportion be explained by the socioeconomic status among care recipients. According to a recent investigation, factors attributable to the organization of care at different levels (the care unit, the management and the responsible authority

levels) seem to be the major cause of variations in healthcare results (Success factors in diabetes care 2014).

Patients with prediabetes or diabetes at early stages will more seldom be given care at the specialized clinics where biobanks for research traditionally are built. It is thus of importance to find a workable model for biobanking in primary care.

1. Screening and Prevention: the project aims to find workable models for early detection and treatment of diabetes and also of its precursor, prediabetes, to prevent further development to manifest diabetes. The golden standards for diagnosis have been either to test fasting plasma glucose or performing an oral glucose tolerance test (OGTT). The latter is resource- and time-consuming for both the patient and the caregiver. A less laborious method, HbA1c (glycosylated haemoglobin), has been approved for the diagnosis of diabetes, but is yet less studied and accepted to use as a test of prediabetes. Determining HbA1c has an advantage over measurements of plasma glucose, since the test result is not affected by a recent meal. For identification of individuals with increased diabetes risk, simple risk surveys, as FINDRISC, have been used (Lindström J et al. 2003). It is unclear if such risk-tests are applicable in people with non-European background, especially together with HbA1c for diagnosis (Martin E et al. 2011). Hence, one important aim of the 4D diabetes project is to evaluate and compare the different screening tools (FINDRISK, HbA1c and fasting plasma glucose/OGTT) in early detection of prediabetes and type 2 diabetes.

The aim of the project beyond method of diagnosis is to create effective means of intervention for prediabetes to prevent or postpone the onset of diabetes. The basis for intervention in prediabetes is lifestyle modification. The methods currently used in Sweden are designed for individuals with Swedish or European background and are not generic for use in people with other dietary and lifestyle habits, which now constitutes a growing high-risk group (Wändell PE et al. 2010). In the current pilot project so far approximately 500 people have performed screening tests. Intervention research is under design focused on personalization as well as stress management. The screening will be extended to care givers with high-risk groups such as dental care and outpatient psychiatry.

To increase statistical power in the validation of a screening method for different ethnic groups, a collaboration with research groups in Malmö and Gothenburg has started. Furthermore, the project is affiliated with SMART2D, a project funded by a Horizon2020 grant (http://ki.se/en/phs/smart2d). Discussions are underway to involve e-health solutions in the intervention models.

2. Primary Care Process: The project focuses on the diabetes care process in primary care. A standard process has been developed for how evidence-based care should be performed by a healthcare team in primary care, from diagnosis to follow-up including collaboration with other healthcare providers. In an initial research project, the care and the operation have been mapped in eight primary care units presenting good and less good results by conventional indicators. The initial mapping of care included multiple patient interviews focusing on the patient's perception of what good care means. The interviews are compiled and results are to be published. A tool for systematic quality assurance procedures has been developed and will be tested as a mean to improve care.

Research within the project is related to the implementation of the care process as well as of the tool for quality assurance within SLL. There is also a preliminary plan for transforming the tool and process to participating countries in SMART2D (Horizon2020), primarily to South Africa and Uganda.

For a patient-centered care process patient-reported outcome measures (PROM and PREM) are required to a greater extent than is now the case. Possibly this can be done in research collaboration with one of the patient-centered e-health projects underway (e.g. PLM 3.0). The Primary care process model is generic for other chronic diseases and if it appears successful for diabetes is the plan to implement the approach for other chronic diseases and possibly to the national level.

3. Building a Biobank: Related to the screening project, logistics of sampling to the Stockholm Medical Biobank are tested. The purpose of this project is to create a model to easily be able to offer patients in primary care participation ("opt-in") in the biobank. Although in this case, the logistics are adjusted for patients screened for prediabetes or type 2 diabetes, but should be generalizable to other patient groups. Biobank 4DT2D includes both healthy controls and individuals with diagnosed prediabetes or diabetes. The associated database contains a thorough characterization of the subjects. Samples from the biobank will be available for multidisciplinary research. The inflow to the biobank is set to about 1000 subjects per year. Since start of the project Q2 2014 over500 samples have been included.

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4D Heart failure

Background

The prevalence of heart failure (HF) is increasing due to an aging population and a better survival from myocardial infarction and is now one of the most common and expensive conditions due to frequent readmissions and high costs for hospital care. However, recent Swedish epidemiologic data show a small but clear decreasing incidence of both chronic and post myocardial infarction heart failure (Zarrinkoub R et al. 2013, Desta L et al. 2015). HF affects 2% of the population and is characterized by severely reduced quality of life, poor life expectancy and frequent exacerbations of acute heart failure. Poor organization of care, lack of use of proper diagnostics and underuse of evidence based highly effective disease modifying therapy (medications, cardiac resynchronization therapy, advanced heart failure care) are underlying structural problems that could be improved for the benefit of the patient and likely to reduce costs for the healthcare system.

Further, the identified knowledge gap in HF is lack of evidence-based therapy for a large group of HF patients, HF with preserved left ventricular function. HF is classified based on presence or absence of LV systolic function as measured by LV ejection fraction (LVEF) into HF with reduced LVEF called HFrEF or HF with preserved LVEF called HFpEF. While HFrEF is decreasing in prevalence and has effective HF treatment with neurohormonal antagonists, the prevalence of HFpEF is increasing (Owan TE et al. 2006) with similar risk for readmissions for HF and mortality as HFrEF and with no established therapy. Compared to HFrEF the HFpEF population is older, has high female representation (Mendes LA et al. 1997, Desta L et al. 2015) and a strong association with atrial fibrillation, hypertension, diabetes and thromboembolism (Owan TE et al. 2006, Mendes LA et al. 1997, McMurray JJ et al. 2012, Donal E et al. 2009, Donal E et al. 2014).

Overall, this may suggest a different pathophysiology for HFpEF versus HFrEF. Is not known whether HFpEF precedes HFrEF or is an entirely separate disease. Furthermore, the LV remodeling process in HFpEF is not well characterized. It appears that the knowledge gap related to the unique pathophysiological features of HFpEF needs to be addressed if effective therapies are to be designed (Gheorghiade M, et al. 2013).

Research agenda

The overall purpose of PREFERS Stockholm (Preserved and reduced ejection fraction epidemiological regional study) is to better define the pathophysiologic mechanisms for HFpEF and to utilize this information to develop an improved therapeutic strategy. The PREFERS study is a joint collaboration with AstraZeneca and Science for Life Laboratory to explore disease mechanisms for HFpEF using new cutting edge techniques like advanced bioinformatics (professor Bengt Persson) and spatial transcriptomics (professor Joakim Lundeberg).

The primary objective is to find:

- unique biomarkers (genes, proteins, metabolites) that differentiate HFpEF from HFrEF
- biomarkers of hemostasis and thrombosis in HFpEF patients with or without atrial fibrillation (AF)
- a correlation between biomarker levels and clinical, echocardiographic, magnetic resonance imaging (MRI) and ECG measures of HFpEF

Methods

The goal of PREFERS is to use advanced imaging, biomarker identification and differential biomolecule display tools in an integrative fashion to clarify the pathophysiologic substrate of HFpEF. Therefore, an epidemiological study to compare HFrEF and HFpEF is warranted. We aim to find relevant biomarkers related to imaging and clinical data in search for new therapeutic targets to prevent or reverse disease.

1. CABG−PREFERS is a myocardial biopsy study where CABG patients are characterized through clinical and imaging descriptions for diastolic and systolic dysfunction and by myocardial biopsies from the right atrium and the right and left ventricles as well as central and peripheral blood during surgery. The study was started in early 2014. The myocardial biopsies will be immediately processed to determine mRNA with single cell technique, to obtain spatial transcriptomics and to analyse gene expression and mapping of cell signalling pathways active in HFpEF and HFrEF. In addition, we will utilize the Human Protein Atlas antibodies against >14500 proteins at SciLifeLab to determine proteins involved in the pathogenesis. The results will regularly be analysed in the scientific multidisciplinary leadership group to further refine the outline and target of our main project. Further analyses including clinical follow up are planned for 2016.

2. The PREFERS study started in December 2014. Gene expression profiles and protein patterns, including those for hemostasis and thromboembolism, will be analysed in peripheral venous blood of de novo HFpEF and HFrEF patients at the Stockholm hospitals. Clinical data, echo−Doppler and ECG will be recorded in all patients to allow for analysis of associations between clinical data and biomarkers. To further explore this, a subset of patients will also do an MRI. The PREFERS−study will use a common characterization and therapeutic application for HFpEF and HFrEF patients for Stockholm made possible by the electronic patient files and the ECG and echocardiographic data file common for the entire Stockholm area (2 million inhabitants) at all levels of care. Serial biomarkers, Doppler−echocardiographic measurements and MRI in selected sub−study patients will be performed.

3. At primary care centers, blood samples from patients with HT with and without HF will be included by clinical evaluation (electronic case history), electrocardiography and echocardiography. Age and sex matched elderly control subjects will undergo similar repeat peripheral venous blood biobanking and imaging starting in 2015. In Hypertension and Control cohorts biomarkers will be analysed for associations towards three groups, similar as in the CABG cohort: patients with normal systolic and diastolic LVEF (controls), those with reduced LVEF (patients that may risk developing HFrEF) and patients with preserved LVEF and signs of diastolic dysfunction (patients that may risk developing HFpEF).

We aim to fill the knowledge gap for HFpEF patients through characterization of and comparison between new onset HFpEF and HFrEF patients by using high quality clinical and imaging data, by known biomarkers for fibrosis, inflammation, hemodynamics (NT−proBNP), hemostasis and thrombosis and by new blood and cardiac biopsy markers through SciLifeLab platforms of genomics, transcriptomics and proteomics. All these data will be explored by state−of−the−art bioinformatics, methods to investigate gene expression patterns, sequence variation, DNA methylation, posttranslational modifications and systems biology approaches including pathway and network analysis.

By the current project we hope to identify new biomarkers of disease progression and to find pathophysiologic mechanisms to support the finding and explorations of new treatment regimens in particular for HFpEF.

		Number of patients (n) per year				
Flow chart		**2015**	**2016**	**2017**	**2018**	**2019**
CABG* - PREFERS	Blood**	70	130			
	Myocardial biopsies	70	130			
PREFERS	Peripheral Blood	100	200	500	1000	2000
Hypertension	Peripheral Blood		100	200	500	1000
Control (PREFERS and Hypertension)	Peripheral Blood		100	100	100	100

*Coronary Artery Bypass Surgery: elective CABG patients in three groups: patients with normal left ventricular ejection fraction (LVEF) (controls), those with reduced LVEF (patients that may risk developing HFrEF and have or lack the clinical heart failure syndrome) and patients with preserved LVEF (patients that may risk developing HFpEF and have or lack the clinical HF syndrome).

**Blood samples from Coronary Sinus, Coronary Artery and peripheral blood

Key improvements of care

Informatics is a key component of the 4D heart failure project, to improve on the care for patients, and to ensure novel solution for capture of information, to bring together information from the different sources both for research and for clinical care.

Below is a short summary of steps in the 4D heart failure project to make infrastructural changes to provide better care for the patients but also to improve the conditions for regional clinically meaningful research in the PREFERS project:

a) **Development of an electronic case-book** with structured data to provide complete national quality registry data and to a research database together with complete data to handle clinical decisions. Additional structured data on imaging and ECG are also provided for the case-book.

b) **Development of a new biobanking facility** within the Karolinska University Laboratory for HF patients treated in Stockholm County Hospitals. The system is up and running in the Karolinska Hospital, robots are presently installed in Danderyd Hospital and the South Hospital.

c) **A joint protocol has been developed** for Stockholm County for diagnosis and treatment of HF with a support from hospital specialists in cardiology, clinical physiology and primary care physicians including protocols for echocardiography and ECG.

d) **Heart failure clinics at the 5 major hospitals** (Danderyd Hospital, Karolinska Solna and Huddinge, South Hospital and Capio St Goran) have been expanded to provide better care for new onset HF patients from the whole region. By using electronic referrals and a joint work program for these clinics we hope to establish HF clinics as hubs for better process of care and individual care plans.

e) **Use of these tools to develop a durable program for earlier diagnosis**, and earlier therapy: The systems for communication with and obtaining information from patients, in combination with PREFERS molecular/genetic data, will allow us to develop "personalized" care and treatment.

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