Second annual meeting

8th November 2022 at 9:00-16:00
The AIAS Auditorium, Aarhus University
Høegh-Guldbergs Gade 6B, 8000 Aarhus C

9:00 **Opening remarks** by Hans Erik Bøtker, Vice-Dean for Research at the Faculty of Health, Aarhus University

Welcome by Anders Børglum, Chair of the Personalised Medicine Network and Professor at the Dept. of Biomedicine, Aarhus University

SESSION I (chair: Anders Børglum)

9:15 **The genetic architecture of depression** Andrew McIntosh, Professor at the Division of Psychiatry, University of Edinburgh, Scotland

9:55 **Improving the clinical value of genetic risk scores** Bjarni J. Vilhjálmsson, Professor at the National Centre for Register-based Research and the Bioinformatics Research Centre, Aarhus University

10:25 **Break, poster viewing and networking**

SESSION II (chair: Signe Borgquist)

11:00 **The national initiatives for implementing Precision Cancer Medicine in Norway**
Molecular heterogeneity in Ductal Carcinoma in Situ Therese Sørlie, Head of the Dept. Cancer Genetics, Oslo University Hospital and Adjunct Professor at the University of Oslo, Norway

11:40 **Toward personalized treatment of immunodeficiencies by targeted gene correction** Jacob Giehm Mikkelsen, Professor at the Dept. of Biomedicine, Aarhus University

12:10 **Flash talks (1-2)**
Identification of women at high risk of postpartum psychiatric episodes (Presenter: Janne Tidselbak Larsen)

Rare coding variants in autism and comorbid subgroups (Presenter: Jinjie Duan)

12:30 Lunch and networking

13:15 **Poster session** (chairs: Doug Speed & Lars Dyrskjøt Andersen)
The poster presenter is asked to give a three-minute oral presentation in English followed by two minutes for discussion. The chairs will select the best poster, which will be awarded a prize.

For an overview of poster presentations, please see next page

SESSION II (chair: Deirdre Cronin Fenton)

14:00 **Introduction to Omics Focus Group** Joanna Kalucka, Assistant Professor at the Dept. of Biomedicine & Christian Damsgaard, Assistant Professor at the Dept. of Biology, Aarhus University

14:05 **Biomarker development for personalized prostate cancer management** Karina Dalsgaard Sørensen, Professor at the Dept. of Clinical Medicine – Molecular Medicine, Aarhus University

14:35 **Brain-first and body-first subtypes of Parkinson's disease** Per Borghammer, Professor at the Dept. of Clinical Medicine – Nuclear Medicine and PET, Aarhus University

15:05 **Flash talks (3-4)**
LDAK-GBAT: fast and powerful gene-based association testing using summary statistics (Presenter: Takiy Berrandou)

Affinity profiling of RNA aptamers on plasma as a potential diagnostic tool for bladder cancer (Presenter: Søren Fjelstrup)

15:25 **Closing remarks and poster award**

15:35 Coffee & cake, poster viewing and networking

OVERVIEW FLASH TALKS & POSTERS

Oral flash talk presentations

Three abstracts are selected for plenary flash talk presentation (see scheme below). The flash talk presenters are asked to give a 5-minutes oral presentation followed by 5 minutes for discussion.
The chairs will select the best flash talk, which will be awarded a prize.

Oral poster session

The poster presenters are asked to give a 3-minutes oral presentation followed by 2 minutes for discussion.
The chairs will select the best poster in each session, which will be awarded a prize.

NUMBER	PRESENTER	TYPE & SESSION	TIME SLOT
1	Janne Tidselbak Larsen	Flash talk, plenary I	12:10 – 12:20
2	Jinjie Duan	Flash talk, plenary I	12:20 – 12:30
3	Takiy Berrandou	Flash talk, plenary II	15:05 – 15:15
4	Søren Fjelstrup	Flash talk, plenary II	15:15 – 15:25
5	Anders Jespersen	Poster, session	13:15 – 13:20
6	Asger Jørgensen	Poster, session	13:20 – 13:25
7	Demet Ozcan	Poster, session	13:25 – 13:30
8	Eske Glud	Poster, session	13:30 – 13:35
9	Merina Shrestha	Poster, session	13:35 – 13:40
10	Shubhangi Das Barman	Poster, session	13:40 – 13:45
11	Xuan Zhou	Poster, session	13:45 – 13:50
12	Yixin Lin	Poster, session	13:50 – 13:55

SPEAKER BIOGRAPHIES

Andrew McIntosh is a Professor of Biological Psychiatry at the Division of Psychiatry, University of Edinburgh and is an NHS Adult Psychiatrist. He co-chairs the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (PGC) and leads the Generation Scotland Expert Working Group for Psychiatric Disorders. He is Chief Scientist of the UK Health Data Research Hub for Mental Health, DATAMIND and leads projects in depression genomics in the UK and Africa.

Bjarni J. Vilhjálmsson is a statistical geneticist and Professor at the National Centre for Register-based Research and affiliated with the Bioinformatics Research Centre at Aarhus University. Bjarni currently leads a research group at Aarhus University that is focused on developing methods that integrate electronic health records and large genetic data to understand psychiatric disorders and other diseases. Bjarni is the author of LDpred1/2, one of the most cited methods and software for deriving Polygenic risk Scores (PRS) and has contributed significantly to the development of the entire PRS field.
Bjarni completed his PhD in Computational Biology from the University of Southern California in 2011 and went on to do postdoctoral research at Harvard School of Public Health, Harvard University, and later at the Bioinformatics Research Centre (BiRC) of Aarhus University. In 2016 Bjarni left academia to work as a software product owner at QIAGEN, but rejoined academia at Aarhus University to establish his own research group. Bjarni was awarded the prestigious Lundbeck Fellow grant in 2020.

Therese Sørlie is head of department of Cancer Genetics, Institute for Cancer Research at Oslo University Hospital. She is also Adjunct Professor at the Institute of Clinical Medicine, University of Oslo. She received her PhD from University of Oslo in 2000 under the supervision of Prof. emerita Anne-Lise Børresen-Dale and she joined Prof David Botstein's group at Stanford University as a postdoctoral fellow from 2001 to work on molecular classification of breast cancer. Her contribution during this time pioneered gene expression profiling of tumors and has resulted in a classification scheme for breast cancer that is implemented in international guidelines for the treatment of breast cancer. In Norway, this classification is now implemented through the participation in two clinical studies, EMIT and OPTIMA. Therese Sørlie has led her own research group at the Institute for Cancer Research since 2012 and from 2017 she has been the head of department of Cancer Genetics. Her early work on breast cancer classification has continued to influence her research that now focuses on studying breast cancer heterogeneity and identifying the molecular mechanisms underlying breast tumor initiation and progression to the intrinsic molecular subtypes, including the transition to invasive breast cancer. Her research group has expertise in molecular biology and bioinformatics and uses both mouse models and patient cohorts in their studies.

SPEAKER BIOGRAPHIES

Jacob Giehm Mikkelsen is a professor at Department of Biomedicine, Aarhus University. His main area of research is development of genetic therapies with particular focus on engineering of molecular tools for gene editing and delivery of gene editing tool kits for therapeutic use. Very often, this work involves understanding and adapting viruses as delivery vehicles. His current interests include treating immunodeficiencies by ex vivo genome editing of hematopoietic stem cells. His research group has also established the use of genome-wide CRISPR screening technologies for multiple purposes including studies of cancer drug resistance, immune regulation, and cell death. Jacob Giehm Mikkelsen did his post doc on gene therapy for hemophilia at Stanford University and was appointed as Professor in genetic engineering and therapy at the Department in 2015. Jacob Giehm Mikkelsen is a member of The Danish Council on Ethics (Det Etiske Råd), appointed by the Committee on the Danish Council on Ethics in the Danish Parliament since 2019, and has contributed to a series of reports from the council including reports on gene-modified organisms and ethics in a new era, genetic modification of future humans and ethics concerns related to the COVID-19 pandemic.

Karina Dalsgaard Sørensen holds a master's degree in Biology and a PhD degree in Molecular Biology from Aarhus University. Since 2010, she has been a group leader at Department of Molecular Medicine at Aarhus University Hospital, where she heads the prostate cancer research group. She is a full professor at Department of Clinical Medicine, Aarhus University, and a recognized authority in the field of translational prostate cancer research.

Per Borghammer is a professor of Nuclear Medicine & Neuroscience, Medical Faculty of Aarhus University. He specializes in clinical imaging of neurodegenerative disorders, in particular Parkinson's disease. Dr. Borghammer's research involves understanding the early and prodromal phase of Parkinson's disease (PD). His research focuses mainly on the etiopathogenesis of PD, in particular the prion-like spreading of alpha-synuclein and whether PD in some cases originates in the peripheral autonomic nervous system. Dr. Borghammer employs a highly multi-disciplinary approach, including in depth characterization of patient cohorts using multi-modality imaging, histological studies of archived patient tissues, epidemiological studies, and mechanistic studies in experimental animal models of PD. In addition, his group is developing a range of PET tracers and other objective imaging markers to study non-motor dysfunction in PD. Most notably, he pioneered the development of novel PET imaging techniques to quantify the loss of parasympathetic innervation to internal organs. Dr. Borghammer's research is funded by the Lundbeck foundation, Michael J. Fox Foundation, Danish Research Council, and Danish Parkinson Association

ABSTRACTS – INVITED SPEAKERS

The genetic architecture of depression

Andrew McIntosh
Professor at the Division of Psychiatry, University of Edinburgh, Scotland

The most recent freeze of the psychiatric genomics consortium (PGC) Major Depressive Disorder working group includes data from more than half a million depressed individuals and 3 million controls. I will present data on the results from this most recent and unpublished freeze, including analyses showing enrichment of expression signals for specific cell types, existing antidepressant treatments and repurposing candidates.

Improving the clinical value of genetic risk scores

Bjarni J. Vilhjálmsson
Professor at the National Centre for Register-based Research and the Bioinformatics Research Centre, Aarhus University, Aarhus

Over the past decade predicting disease risk and traits from individual genotypes has received increased attention in human genetics. This development has been driven by ever larger genetic datasets, such as UK biobank and publicly available summary statistics from large genome wide association studies (GWAS), which has generally translated into more predictive polygenic scores (PGS). However, for most common diseases and disorders, their predictive accuracy is still far from the theoretical upper limit determined by the heritability. Furthermore, the accuracy of PGSs is often severely reduced in individuals of non-European genetic ancestry, which could exacerbate health disparities if used in clinical applications. Here I will highlight these limitations and demonstrate how integrative Bayesian and Machine Learning methods could help address these.

The national initiatives for implementing Precision Cancer Medicine in Norway
Molecular Heterogeneity in Ductal Carcinoma in situ

Therese Sørlie
Head of the Dept. Cancer Genetics, Oslo University Hospital and Adjunct Professor at the University of Oslo, Norway

Precision Medicine is really all around us and in the first part of this presentation I will talk about the initiatives for implementing precision cancer medicine in Norway. In the last few years, there has been a great effort nationwide to build an infrastructure for precision diagnostics, initiate a clinical trial to harmonize access to genomic testing and off-label use of cancer drugs, and to secure reimbursement to patients via public-private partnerships. I will briefly describe the different pillars of this initiative and the current status.

ABSTRACTS – INVITED SPEAKERS

In the second part, I will talk about our studies of molecular heterogeneity in Ductal Carcinoma In Situ (DCIS). DCIS is extremely heterogeneous and morphologically diverse; however, this is usually not taken into account in diagnostics. Almost all patients are treated with surgery and radiation therapy that comes with a high risk of over-treatment. My group has been studying DCIS using genomic approaches and we have found that the intrinsic breast cancer subtypes, defined for invasive carcinomas, are also present in DCIS. I will present how we study DCIS in a subtype-specific manner, and how this may have implications for more precise treatment of these pre-invasive lesions in the future.

Toward personalized treatment of immunodeficiencies by targeted gene correction

Jacob Giehm Mikkelsen
Professor at the Dept. of Biomedicine, Aarhus University

Personalized medicine is an approach to health care based on each individual's unique genetic makeup. Novel genome editing technologies offer the possibility to correct disease-causing gene variants and are already being explored as personalized medicines. Still, translation into the clinic awaits further studies of efficacy and safety, and novel ways of delivering gene editing tool kits to cells and tissues are needed. The vision is to generate gene editing drugs that can fix genomic errors within days and then vanish. I will discuss some of the strategies that we are currently working on in Aarhus to push gene editing as a treatment of immunodeficiencies forward as precision medicine. Such strategies include both gene editing based on homology-directed repair as well as prime editing. Our studies include efforts to achieve potent gene editing in hematopoietic stem cells, but also novel approaches for delivering 'ready-to-go' genome editing tool kits in revamped virus particles for potential in vivo use.

Biomarker development for personalized prostate cancer management

Karina Dalsgaard Sørensen
Professor at the Dept. of Clinical Medicine, Aarhus University & the Dept. of Molecular Medicine, Aarhus University Hospital

Prostate cancer (PC) is the most common non-skin cancer and a major cause of cancer-associated mortality among men in Western countries, including in Denmark. PC is characterized by extensive molecular heterogeneity that is also reflected in highly variable disease courses. While some tumors progress to metastatic life-threatening disease, other tumors remain indolent with no significant effect on the patient's health during his lifetime. Furthermore, the currently used prognostic tools for PC risk stratification are inaccurate, leading to undertreatment of aggressive PC and overtreatment of non-aggressive PC. Hence, new biomarkers are needed to facilitate a better and more personalized treatment approach. In order to identify such novel

aggressiveness biomarkers, we have performed molecular profiling analyses of PC samples from representative clinical cohorts, combining bulk tumor RNA sequencing and spatial molecular analyses to examine multiple aspects of PC biology, including the role of the tumor immune microenvironment and the microbiome for PC progression.

Brain-first and body-first subtypes of Parkinson's disease

Per Borghammer
Professor at the Dept. of Clinical Medicine – Nuclear Medicine and PET, Aarhus University

Parkinson's disease (PD) is a heterogenous disorder. At the time of diagnosis, patients can show highly variable patterns of symptoms and objective neuronal dysfunction. Such subtypes of PD have varying prognoses and progression rates of the disease. Some patients develop a host of symptoms from the autonomic symptom years before diagnosis, whereas others do not have any autonomic symptoms when the parkinsonism emerges.
The brain-first and body-first hypothesis proposes that the initial formation of PD-related pathology can arise in different parts of the nervous system, and that the pathology then spreads from the onset site in a prion-like manner. An origin in the nervous system of the gut leads to a body-first clinical type, characterized by prodromal autonomic and sleep problems. In contrast, the brain-first type may originate in the olfactory bulb or limbic system. This type has very few or no 3 prodromal symptoms before parkinsonism emerges. This staging scheme may have potential for personalized interventions and disease-modification in PD.
This lecture presents the underlying evidence for the brain- vs- body-first hypothesis, including data from clinical patient studies, animal models, post mortem studies, and epidemiology.

ABSTRACTS – FLASH TALKS

1 Identification of women at high risk of postpartum psychiatric episodes

Benedicte M. W. Johannsen [(1)], **Janne Tidselbak Larsen* [(1)]**, Xiaoqin Liu [(1, 2)], Kathrine Bang Madsen [(1)], Merete Lund Mægbæk [(1)], Clara Albiñana [(1)], Veerle Bergink [(3)], Thomas M. Laursen [(1, 2, 4)], Bodil H. Bech [(5)], Preben Bo Mortensen [(1, 2)], Merete Nordentoft [(2, 6, 7)], Anders D. Børglum [(2, 8, 9)], Thomas Werge [(2, 10, 11, 12)], David M. Hougaard [(2, 13)], Esben Agerbo [(1, 2, 4)], Liselotte Vogdrup Petersen** [(1, 2, 4)], Trine Munk-Olsen** [(1, 14)]

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10. Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Denmark
11. Department of Clinical Medicine, University of Copenhagen, Denmark
12. LF Center for GeoGenetics, GLOBE Institute, University of Copenhagen, Denmark
13. Statens Serum Institut, Copenhagen, Denmark
14. Psychiatric Research Unit, Institute for Clinical Research, University of Southern Denmark, Denmark

Background
We quantified relative and absolute risks of postpartum psychiatric episodes (PPE) following risk factors: Young age, past personal or family history of psychiatric disorders, and genetic liability.

Methods
We conducted a register-based study using the iPSYCH2012 case-cohort sample. Exposures were personal history of psychiatric episodes prior to childbirth, being a young mother, having a family history of psychiatric disorders, and a high (highest quartile) polygenic score (PGS) for major depression. PPE was defined within 12 months postpartum by prescription of psychotropic medication or in- and outpatient contact to a psychiatric facility. We included primiparous women born 1981 - 1999, giving birth before January 1st, 2016. We conducted Cox regression to calculate hazard ratios (HRs) of PPE, absolute risks were calculated using cumulative incidence functions.

Results
We included 8,174 primiparous women, and estimated baseline PPE risk was 6.9% (95% CI 6.0-7.8%, number of PPE cases: 2,169). For young mothers with a personal *and* family history of psychiatric disorders, the absolute risk of PPE was 21.6% (95% CI 15.9-27.8%). Adding information on high genetic liability to depression, the risk increased to 29.2% (95% CI 21.3-38.4%) for PPE.

Conclusions
Information on prior personal and family psychiatric episodes as well as age may assist in estimating a personalized risk of PPE. Furthermore, additional information on genetic liability could add even further to this risk assessment.

ABSTRACTS – FLASH TALKS

2 Rare coding variants in autism and comorbid subgroups

Jinjie Duan[1,2,3], Jakob Grove[1,2,3,4], F. Kyle Satterstrom[5,6,7], Jack Fu[7,8,9], Caitlin Carey[5,6], Jiebiao Wang[10], iPSYCH-Broad Consortium, Autism Sequencing Consortium, Bernie Devlin[11], Kathryn Roeder[16,17], Joseph Buxbaum[12], Elise Robinson[5,6,13], Michael Talkowski[5,7,8,9,15], Mark Daly[5,6,7,14], Anders D. Børglum[1,2,3]

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Autism spectrum disorder (ASD) is highly heritable and heterogenous, often presenting with comorbid conditions including intellectual disability (ID), attention deficit hyperactivity disorder (ADHD), epilepsy, anxiety, depression, etc. However, the rare-variant genetic architecture of ASD with and without comorbid conditions is unclear. Here we analyze rare coding variants in ASD and comorbid subgroups, to explore the shared and distinct genetic architecture for ASD and comorbid subgroups.

First, we report on the largest ASD exome sequencing study to date (28,467 cases + 48,778 controls) which combines the latest iPSYCH exomes with data collections from the Autism Sequencing Consortium (ASC), the Simons Simplex Collection (SSC), and Simons Powering Autism Research for Knowledge (SPARK). We incorporated SNVs, indels, and CNVs to increase the power of gene discovery, and identified 185 genes (41 novel) associated with ASD with FDR < 5%.

For the analysis of comorbid subgroups, we focused on the iPSYCH cohort, in which the diagnoses are linked with clinical data from the Danish register system. We performed burden analyses of rare variants with high and moderate impact respectively, for multiple gene sets including our identified ASD genes, Deciphering Developmental Disorder genes, and neurodevelopmental disorder genes. The analyses were also performed across ASD cases with and without ID and a line-up of other comorbidities including ADHD, schizophrenia, and 7 other psychiatric disorders.

Across all tested gene sets, both high and moderate-impact variants were significantly enriched in ASD cases regardless of ID and other comorbidities, relative to controls. We observed that cases with ID showed a significant enrichment relative to cases without ID. In contrast, compared to cases without any comorbidity, cases comorbid with other psychiatric disorders did not show an increased burden, even cases with multi

morbidity. A single exception was observed for moderate-impact variants, which revealed an increased burden in cases comorbid with schizophrenia relative to cases without schizophrenia. The results suggest that the high-impact rare variants might confer more general psychopathology liability while moderate-impact rare variants might influence the development of psychiatric disorders more specifically.

3 LDAK-GBAT: fast and powerful gene-based association testing using summary statistics

Takiy Berrandou [1*], David Balding [2], Doug Speed [1]

[1]*Quantitative Genetics and Genomics (QGG), Aarhus University, Aarhus, Denmark.*
[2]*Melbourne Integrative Genomics (MIG), Melbourne University, Melbourne, Australia.*

Genome-wide association studies (GWAS) test each SNP individually for association with the phenotype. However, it is now recognized that gene-based analyses - which jointly test sets of SNPs for association with the outcome - can complement single-SNP analysis and provide additional insights for the genetic architecture of complex traits.

Here, we propose LDAK-GBAT, a new tool for gene-based association analysis that requires only summary statistics from GWAS and a reference panel.

We first evaluate the performance of LDAK-GBAT and alternative tools such as MAGMA, GCTA-fastBAT and sumFREGAT (which implemented SKAT-O, PCA and ACAT methods) using 14 traits from UK Biobank. We show that LDAK-GBAT is computationally efficient, taking approximately four minutes to analyze imputed data (>7.1 million SNPs) when using a reference panel of 404 individuals. It also produces *P* values that are well-calibrated under the null and is robust to the choice of reference panel. LDAK-GBAT finds more significant genes than the five other tools. For example, LDAK-GBAT finds on average 25% more significant genes than sumFREGAT-PCA, the second best-performing method. Next, we apply LDAK-GBAT to 18 traits from the Million Veterans Project and nine traits from the Psychiatric Genetics Consortium. In total, we find 6,083 significant genes, which is 46% more than found by single-SNP analysis, and 55% more than MAGMA the largely used tool for gene-based association analysis.

In conclusion, our proposed tool, implemented in our freely available software LDAK (www.ldak.org/), has the potential to identify additional novel disease-susceptibility genes for complex diseases from GWAS datasets.

ABSTRACTS – FLASH TALKS

4 Affinity profiling of RNA aptamers on plasma as a potential diagnostic tool for bladder cancer

Søren Fjelstrup[1†], Daniel M. Dupont[1†*], Claus Bus[1], Jan J. Enghild[2], Jørgen B. Jensen[4,5], Karin Birkenkamp-Demtröder [3,5], Lars Dyrskjøt[3,5], Jørgen Kjems [1,2*]

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The molecular composition of blood is a signature of human health, reflected in the thousands of blood biomarkers known for human diseases. However, establishing robust disease markers is challenging due to the diversity of individual samples. New sequencing methods have simplified biomarker discovery for circulating DNA and RNA while protein profiling is still laborious and costly. To harness the power of high-throughput sequencing to profile the protein content of a biological sample, we developed a method termed APTASHAPE that uses oligonucleotide aptamers to recognize proteins in complex biofluids. We selected a large pool of 2'Fluoro protected RNA sequences to recognize proteins in human plasma and identified a set of 33 cancer-specific aptamers. Differential enrichment of these aptamers after selection against 1 µL of plasma from individual patients allowed us to differentiate between healthy controls and bladder cancer-diagnosed patients (91% accuracy) and between early non-invasive tumors and late stage tumors (83% accuracy). Affinity purification and mass spectrometry of proteins bound to the predictive aptamers showed the main target proteins to be C4b-binding protein, Complement C3, Fibrinogen, Complement factor H and IgG. The APTASHAPE method thus provides a general, automated and highly sensitive platform for discovering potential new disease biomarkers.

ABSTRACTS – POSTERS

5 GWAS of clinically predicted suicide liability

Anders Jespersen, Oleguer Plana-Ripoll, Jette Steinbach, Clara Albiñana, John McGrath, Preben Mortensen, Florian Privé, Esben Agerbo, Bjarni Vilhjálmsson

Aarhus Universitet, Aarhus, Denmark

Suicide accounts for 1 in every 100 deaths worldwide, resulting in more than 700,000 deaths annually. Globally the number of suicides has decreased by 36% in the last 20 years whilst in the Americas have seen a 17% increase in deaths by suicide. Risk factors include previous suicide attempt, depression, and alcohol use disorders. However, there is considerable evidence that attempted suicide and death by suicide have distinct etiologies.
Heritability estimates of suicidal behavior range from 17% to 55% suggesting a significant genetic component to suicide risk. Unfortunately, an insufficient number of genotyped cases has caused a lack of adequately powered genetic studies of death by suicide.
We will address this limitation by leveraging Danish electronic health care records to perform a Genome Wide Association Study of clinically predicted suicide liability.

Danish electronic health registers containing all hospital admissions, diagnoses, and prescriptions of the population of Denmark will be used to clinically predict death by suicide. In this analysis we will use a genotyped subsample of the Danish population comprising 323,000 individuals, 869 of whom died by suicide. This sample will be split into a 80/20 training/testing dataset.
A LASSO regression will be applied to obtain predictive weights for more than 400 clinical variables. The resulting weights will be used to clinically predict suicide liability in our testing dataset. We will then perform a GWAS of the clinically predicted suicide liability. Genetic overlap with the most recent case-control GWAS of death by suicide will be investigated, as well as genetic correlations between clinically predicted suicide liability and major psychiatric disorders.

Results from this study will shed light on the contribution of common genetic variants to the clinically predicted risk of death by suicide. Result will demonstrate the level of genetic similarity between clinically predicted death by suicide and observed death by suicide. Finally, this method of leveraging electronic health records for clinical prediction to increase power in genetic studies could pave the way for genetic studies of phenotypes otherwise suffering from low number of genotyped cases.

6 Aptamer-based blood profiling for diagnosis, treatment evaluation and disease severity prediction

Daniel Miotto Dupont[1], Søren Fjelstrup[1], **Asger Jørgensen[1]**, Claus Bus[1], Mikkel Kjær[4], Henning Grønbæk[4], Christian Vægter[3], Nadia Goncalves[3], Thomas Benfield[5], Peter Garred[6], Maria Møller[5], Simone Israelsen[5], Håkon Sandholdt[5], Cecilie Hansen[6], Rasmus Thomsen[7], Natasha Michaelsen[7], Peter Heegaard[8] and Jørgen Kjems[1,2].

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ABSTRACTS – POSTERS

The molecular composition of blood is a reflection of our physiology, health state, lifestyle etc., in many ways a highway of biological information difficult to access. We developed a novel technology, APTASHAPE, to translate this "difficult-to-read" language into readable digital information. APTASHAPE involves the use of panels of small biosensor molecules, 2'-fluoro protected RNA aptamers, to generate imprints of the protein and metabolite signature in a plasma sample. We applied APTASHAPE to profile different cohorts of samples from patients and animal models, and here we present our results in relation to diagnosis and treatment evaluation within Non-Alcoholic Fatty Liver Disease (NAFLD) as well as prediction of clinical disease severity for patients hospitalized following SARS CoV-2 infection. The technology possesses the potential to measure several disease conditions simultaneously based on a single drop of blood (1 microliter of plasma) and can serve as a health-state measuring and prediction tool. The APTASHAPE technology allows individual evaluation of patients and tailors personalized medicine based on the molecular composition of the patient's blood.

7 Association between tumor immune response and risk of recurrence in breast cancer patients treated with radiotherapy

Demet Özcan[1], Lise Thorsen[2], Therese Sørlie[3], Birgitte Offersen[2], Trine Tramm[1]

[1]Pathology, Aarhus University Hospital, [2]Oncology, Aarhus University Hospital, [3]Cancer Genetics, Oslo University Hospital

Background:

More than 75% of newly diagnosed breast cancer (BC) patients receive radiotherapy (RT), but benefit from RT is heterogeneous and not all patients gain survival benefit. Recent studies of the DBCG82bc (Danish Breast Cancer Group) cohort of high-risk BC patients randomized to +/- RT after mastectomy have shown that high level of tumor infiltrating lymphocytes (TILs) are associated with improved overall survival in patients treated with RT.

The aim of this PhD study is to investigate, if presence and/or composition of immune cells (IC) in pretreated tumor tissue is associated with risk of recurrence in BC patients treated with RT.

Material:

The study is planned as a case-control study (400 cases with recurrence: 1000 controls without recurrence) based on three well-described DBCG cohorts (HYPO and IMN2) of patients treated with RT. Formalin fixed, paraffin-embedded tissue from primary tumor and recurrences will be collected from all 1400 patients, and clinical outcome data will be obtained.

Study 1:

The composition of specific IC in primary tumors of various subtypes will be characterized using multiplex immunohistochemistry and digital image analysis.

Study 2:

In the 400 cases, possible differences in immune response and subtype in corresponding pairs of primary tumor and recurrences will be examined.

In a subgroup of patients with both local and distant recurrences available, gene-expression analysis of immunogenic pathways will be performed to explore changes in immune response.

Study 3:
Results from the histopathological analyses will be correlated with clinical outcome data for all 948 patients to examine associations between the immune response in primary tumor and risk of recurrence in BC patients treated with RT.

Perspectives:
If the immune response in the pretreated primary tumor can predict clinical outcome in BC patients, it may lead to more individualized treatment including possible modification of DBCG RT-treatment guidelines.

8 Multicenter Study for Evaluation and Development of New Liquid Biomarkers for Early Detection of Prostate Cancer

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Background
Prostate cancer (PC) is the most commonly diagnosed malignancy and the second leading cause of cancer-association mortality among men in Denmark. While early-stage asymptomatic PC can be cured by surgery and radiotherapy, advanced PC is incurable. Thus, early detection is critical to save lives, but many newly diagnosed PCs are clinically insignificant (non-aggressive) and would remain asymptomatic throughout the patient's life, even if left untreated. Magnetic resonance imaging (MRI) has recently been implemented to guide biopsies of suspect lesions, improving diagnosis accuracy but it remains an expensive procedure with limited capacity at the Danish hospitals. Hence, there is an urgent need for a biomarker test capable of pre-selecting patients in need of a prostate MRI scan and potentially identifying the patients with aggressive PC in need of urgent therapy.

Methods
We will recruit 2.500 men with suspicion of PC, who are referred to a prostate MRI scan at Aarhus University Hospital (AUH), Herlev & Gentofte Hospital (HGH), or Odense University Hospital (OUH), and having a subsequent targeted biopsy of any suspicious lesions. Prior to MRI results, blood and urine will be collected, and the expression levels of a panel (uCaP) of previously identified microRNAs (miR-222-3p, miR-24-3p, and miR-30c-5p), found in urine, quantified. Furthermore, the panel will be sought optimised through miRNA sequencing and identification of new differentially expressed miRNAs between aggressive and non-aggressive PC. Finally, we wish to explore the T-cell receptor (TCR) repertoire in the PC patients through DNA-based TCR sequencing.

Results

Pilot study results in a cohort of 34 men undergoing MRI demonstrated uCaP's ability to outcompete prostate specific antigen (PSA) in detecting aggressive PCs with an AUC of 0.76 versus the AUC of 0.51 for PSA, resulting in a reduction of false positives by 47 %. Meanwhile the same number of aggressive PCs were detected. Recruitment for the current study is actively occurring at The Department of Urology in Aarhus with HGH and OUH soon to follow.

Conclusion

While preliminary results have indicated strong potential for the uCaP panel to have a clinical impact, further validation is needed. Furthermore, identification of novel liquid biomarkers may improve PC diagnosis accuracy and subsequent well-being of patients.

9 Fine Mapping Approaches based on Bayesian Linear Regression Models

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Fine mapping identifies the underlying causal genetic variants and is essential for the future of precision medicine. The aim of our study was to investigate influence of the choice of prior for marker effects, marker set definition, and marker set association statistics on power and precision of Bayesian linear regression (BLR) models fine mapping approach.

We simulated ten replicated quantitative traits, using UK Biobank (UKB) genotypes (533,679) for 335,744 White British Unrelated individuals, from low (GA1) to moderate (GA2) polygenicity with heritability of 30%, and proportion of causal SNPs, 0.1%, 1% and 5%. Marker effects estimated using linear regression were fitted in BLR models along with sparse LD matrix constructed from the UKB genotypes. Prior distributions of the marker effects ranged from low (BayesC) to moderate (BayesR and BayesA) to high (BayesN) polygenicity. Marker sets were constructed based on LD thresholds ($r^2 > 0.7$ and $r^2 > 0.5$), physical and genetic map. Two association statistics was defined, the sum of genetic variance (T_{VAR}), and the sum of posterior inclusion probability (T_{PIP}). F1 classification score (F1) was estimated to evaluate the fine mapping approach.

The highest average F1 (avg. F1) for T_{VAR} was observed for BayesC and BayesR in GA1: 0.686 and 0.684 and GA2: 0.661 and 0.660, respectively (*p-value* < 0.001). For T_{PIP}, BayesC showed highest avg. *F1*:0.596 (GA1) and 0.555 (GA2) (*p-value* < 1×10^{-5}). BayesC and BayesR showed similar avg. *F1*:0.681 and 0.684 respectively in GA1, and 0.652 and 0.659 in GA2 (*p-value* < 0.001). A higher LD threshold ($r^2 > 0.7$) resulted in higher avg. *F1* across all marker effect priors and marker set association statistics in the GA1 and GA2 scenarios.

Preliminary results suggest influence of marker sets definition, the prior distributions, and type of marker set association statistic on the BLR fine mapping approach.

ABSTRACTS – POSTERS

10 Long-duration spaceflight induces gene expression changes in mice

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Long-duration spaceflight causes deleterious changes that are currently inhibitory to sending humans to Mars. Spaceflight induces changes in both the human body and in the bodies of rodent models. These include muscle and bone atrophy, cardiovascular weakening, systemic inflammation, radiation-induced mutagenesis, and exposure to high CO_2. Without effective counter measures like exercise and therapeutic medicine, these changes can result in bone loss, immune dysfunction, cardiovascular deconditioning, and loss of skeletal muscle mass and strength, to name a few consequences. We sent mice to space and on return to Earth, we processed different tissues for single cell RNA sequencing. Here, we perform in-depth cell annotation using excellxgene. We find changes in the relative abundance of stem cells and immune cells across different tissues. Moreover, differential gene expression analysis highlights changes in protein and RNA turnover. Our initial results indicate significant molecular changes after long-duration spaceflight which may impact stem cell function.

11 A novel method for detecting confounding in genome-wide association studies (GWAS)

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Background: GWAS test statistics can be confounded by population stratification due to ancestral and geographic differences between individuals. Most methods for detecting this confounding (most notably genomic inflation and LD Score Regression) assume that population stratification causes constant inflation of test statistics.

Here we hypothesize the alternative. We reason that population stratification creates linkage between SNPs outside their LD blocks, which varies across the genome; variation in this linkage would therefore be indicative of the extent of inflation induced by population stratification. We tested this hypothesis and proposed a new method for detecting inflation due to population stratification.

Methods: For ~ 337k unrelated white British from the UK Biobank, we simulated phenotypes with zero heritability but varying levels of confounding due to either ancestry or birth location. Having performed single-SNP analysis for each simulated phenotype, we show that the inflation of chi-squared test stastitics correlates with levels of long-range linkage, measured using (r_j^2) ¯, the mean squared correlations between each SNP and 10k SNPs randomly drawn from other chromosomes. Thus we propose detecting inflation by regresssing chi-squared test statistics on (r_j^2) ¯. Under the null (i.e., no inflation), the slope from this regression should equal zero, whereas a positive slope indicates inflation.

Results: We show that test statistics of confounded GWAS are inflated, and the extent of inflation varies as a function of (r_j^2) ¯. Regressing chi-squared test statistics on (r_j^2) ¯ detected the inflation (all $p<0.001$ for the slope); and more importantly, yielded inflation estimates that closely track expected inflation for each SNP. In contrast, LD score regression underestimated the inflation.

Conclusions: Inflation of GWAS test statistics due to population stratification varies across the genome depending on linkage between distant SNPs. By exploiting this dependency, the proposed method provides more accurate inflation estimates than LD score regression.

12 Constructing a pipeline for calling SNPs from deep, targeted cfDNA-seq data

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Detection of circulating tumor DNA in blood increasingly attracts attention as a cancer biomarker. For instance, early and reliable detection of cancer mutations in blood may enable early detection of relapse and adjustment of treatment based on the tumor mutational landscape. Yet accurate detection of tumor mutations in deep, targeted sequencing of cell-free DNA remains challenging as the low frequency of mutations in blood makes them hard to discriminate from background signals such as artifacts generated from the sequencing process. To identify variants present in deep, targeted cfDNA-seq data, we are developing a pipeline for tumor/normal paired datasets to call low-frequency somatic variants with high sensitivity and specificity, especially for UMI-seq data. The pipeline constitutes of three main steps: alignment, UMI consensus creation, and variant calling. We compared different UMI consensus strategies and five variant calling algorithms. This work could improve the quality of deep, targeted cfDNA-seq analysis and enables its widespread adoption in the clinic.