AARHUS
UNIVERSITY
DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Biomarkers are revolutionizing drug discovery and the practice of medicine. In Denmark, the unique capabilities **to link biospecimens** with the clinical histories of patients can **revolutionize studies** of the natural history of diseases and the assessment of the **effectiveness of therapies** in real world clinical practice

Biomarkers – a step towards precision medicine

Physicians have always sought to treat the patient, not the disease, based on intuition, clinical experience, or patient characteristics. We live in an age of precision medicine, which will bring us closer to tailored treatments for each patient. Biomarkers are an inherent part of this process, enabling the identification of precise treatment targets.

Supporting evidence-based medicine has always been a mission of clinical epidemiology. To elicit meaningful inferences about relevant patient outcomes, linkage of data on an individual's biomarker information to his or her clinical characteristics and prognostic outcome is essential and is becoming possible.

For more than 40 years, some 200 population-based registries and databases in Denmark have been routinely accumulating data on births, deaths, hospital admissions, procedures, prescription medications and demographics for several generations of Danish residents. These data are collected from real world clinical practice, in a setting of universal and income-independent access to health care, with complete lifetime follow-up.

The Danish National Pathology Registry and Patobank contain detailed nationwide records of all pathology specimens analyzed in Denmark since 1997. Specimens from some pathology departments date back to the 1960s. These archived biospecimens can be traced back on an individual level to data on the same patients stored in population-based and medical registries and databases. This unique network contributes to a new standard in epidemiologic research and large scale longitudinal biomarker studies.

Researchers at the Department of Clinical Epidemiology (DCE), Aarhus University, with vast collective clinical, epidemiologic, laboratory and statistical expertise, are in a unique position to embrace biomarker-based epidemiology as a powerful research tool.

This brochure provides an introductory overview of DCE's biomarker-related research expertise. DCE has an international collaborative network and is always open to new research ideas and opportunities.

A nation of data – a world of opportunities

Denmark has a long tradition of meticulous record keeping, originating in church records and culminating in a large network of routine population registries covering all areas of life and health. Since 1968, each person born in or immigrating to Denmark receives a personal unique identifier, which is used in all records and which makes all data linkable on an individual level.

Residents of Denmark enjoy universal tax-funded access to health care, with health encounters in primary and hospital sector routinely registered in Denmark's various registries and databases. The recorded information includes diagnoses, prescriptions, diagnostic tests, surgical procedures and biomarkers. In fact, biomarkers are recorded through all life stages, from blood spots collected at birth for neonatal screening to biospecimens harvested from terminally ill cancer patients.

Individual linkage, universal health care access, and vast amounts of routinely collected data make Denmark a dynamic and growing cohort of nearly 6 million people as of 2017, with clinical, biomarker and socioeconomic data and complete follow-up.

Danish medical databases provide researchers with a rich source of medical and genetic information, most of which is accessible for research.

REGISTRIES

- Danish Civil Registration System
- Danish National Patient Register
- Danish National Prescription Database
- Danish Medical Birth Registry
- Danish Cancer Registry
- Electronic Health Records
- Danish National Psychiatric Research Registry
- Socioeconomic data (education, income)
- Educational attainment

BIOMARKER DATA

- The Danish National Biobank
- The Danish National Pathology Registry and Pathology Data Bank
- The Danish Cancer Biobank
- The Clinical Laboratory Information System Research database (LABKA)
- The Danish National Neonatal Screening Biobank
- Local hospital and research project biobanks
- Disease-specific biobanks
- Registries of Genetic Diseases

SELECTED DANISH CLINICAL QUALITY DATABASES
(FROM ALMOST 70 DATABASES)

- Urological malignancies
- Gynecological malignancies
- Gastrointestinal cancer
- Lung cancer
- Hematological malignancies
- Breast cancer
- Diabetes

Studies conducted by DCE researchers using data on biomarkers

BREAST CANCER RECURRENCE

CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. JNCI 2011; 103: 489-500.

- **AIM:** Tamoxifen is an important component of endocrine therapy in breast cancer patients. Cytochrome P450 (CYP) enzymes metabolize tamoxifen; CYP2D6 may be a key component of this metabolism. Inherited differences or competitive drug inhibition can lead to differences in CYP enzyme activity, and so may predict response to tamoxifen therapy. This study examined the association of CYP2D6 mutations and CYP2D6 pharmacologic inhibitors with breast cancer recurrence.
- **RESULTS:** This study included 1682 breast cancer patients. Archived breast tumor tissue blocks provided a source of DNA for genotyping. Individual-level linkage across Denmark's network of population-based medical registries enabled correlation of genotyping with tumor estrogen receptor status, patient prescription history and patient outcomes. This study found little evidence of an association between CYP2D6 enzyme inhibition and recurrence in tamoxifen-treated women with breast cancer.
- **SOURCES OF DATA:** Danish Breast Cancer Group, Danish National Pathology Registry and Patobank, Danish National Prescription Registry, Danish National Patient Registry and Danish Civil Registration System.
- **PERSPECTIVES:** Findings can provide reassurance to breast cancer patients treated with tamoxifen.

PREDICTING OCCULT CANCER

Elevated plasma vitamin B12 levels as a marker for cancer: a population-based cohort study JNCI 2013; 105: 1799-1805.

- **AIM:** Vitamin B12 (cobalamin) is an essential nutrient involved in one-carbon metabolism and cell division. Some previous research suggests that elevated B12 correlates with increased cancer risk. This study assessed the clinical implications of elevated vitamin B12 levels in diagnosing cancer.
- **RESULTS:** This study included 333,667 individuals. Cancer risk increased with higher vitamin B12 levels. Analysis of population based data on cancer and routine laboratory testing showed that high plasma vitamin B12 levels may be a marker of undiagnosed cancer.
- **SOURCES OF DATA:** Laboratory Information Systems Database (LABKA), Danish Cancer Registry, Danish National Patient Registry and Danish Civil Registration System.
- **PERSPECTIVES:** High vitamin B12 levels correlated with the risk of subsequently diagnosed cancer, mainly within the first year of follow-up. This may have clinical implications for the interpretation of high vitamin B12 levels.

INFEC
ALZHEIMER
MULTIMORBIDITY
CARDIOVASCULAR D
PATIENT JOURNEYS **RE**
BIOMARKERS PHA
BIOBANKS PRAGMAT
MEDICAL HISTORY **EVIDE**
DIABETES INDIVIDUAL-LEVE
KIDNEY DISEASE **CLINIC**
EARLY DETECTION
COMPARATIVE EFFECTIV
PRECISION MEDICIN
ELECTRONIC HE
TAILORED T
CAN

SERRATED POLYPS ARE CANCER PRECURSORS

Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology 2016; 150: 895-902.

- **AIM:** Most colorectal cancers develop via an adenoma-carcinoma sequence. This study investigated the risk of colorectal cancer among patients with a history of serrated polyps in a nationwide population-based setting.
- **RESULTS:** This study included 2045 colorectal cancer cases and 8105 controls. Findings suggested that patients with a history of serrated colorectal polyps have an increased risk for colorectal cancer. Furthermore, their level of risk is similar to or even higher than that for patients with a history of adenomatous polyps.
- **SOURCES OF DATA:** Danish Cancer Registry, Danish National Pathology Registry and Patobank, Danish National Patient Registry, and the Danish Civil Registration System.
- **PERSPECTIVES :** These findings support existing surveillance guidelines recommending the complete removal of serrated polyps and close follow-up evaluations of patients with these lesions.

INFECTIOUS DISEASES

Mannose-binding lectin gene, MBL2, polymorphisms are not associated with susceptibility to invasive pneumococcal disease in children. Clin. Infect. Dis. 2014; 59: 66-71.

- **AIM:** Mannose-binding lectin (MBL) is a proinflammatory protein involved in complement activation via the lectin pathway in the innate immune system, and the complement system provides immediate host defense against infection. Genetic variation leads to differences in plasma MBL concentrations. Low serum levels of MBL have been associated with a 5-fold increased risk of death due to pneumococcal disease.
- **RESULTS:** This study included 2,372 individuals who were genotyped and assigned MBL2 diplotypes. Children with defective MBL2 diplotypes were not at higher risk for meningitis or bacteremia compared with those with wildtype MBL2.
- **SOURCES OF DATA:** Danish Neonatal Screening Biobank, National Neisseria and Streptococcus Reference Laboratory, Danish National Patient Registry, and the Danish Civil Registration System.
- **PERSPECTIVES:** Findings suggested that defective MBL2 polymorphisms do not predict increased invasive pneumococcal disease in children.

HEMATOLOGY: BIOMARKERS IN RARE HEMATOLOGIC DISEASE

Bone marrow reticulin and collagen content in patients with adult chronic immune thrombocytopenic purpura: a Danish nationwide study. Am J Hematol 2010; 85: 930-934.

- **AIM:** Primary immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by antiplatelet antibody-mediated thrombocytopenia without any obvious initiating and/or underlying cause. This study quantified the reticulin and collagen fiber content in archived bone marrow specimens from patients diagnosed with ITP in Denmark and examined its association with specific clinical characteristics of ITP.
- **RESULTS:** Reticulin and collagen content in the bone marrow correlated with treatment of patients with chronic immune thrombocytopenic purpura.
- **SOURCES OF DATA:** Danish National Patient Registry, Danish National Pathology Registry and Patobank, and the Danish Civil Registration System.
- **PERSPECTIVES:** These findings suggest that bone marrow reticulin and collagen content in chronic ITP patients may be associated with some clinical characteristics.

Expertise in biomarker research

The Department of Clinical Epidemiology was established in 2000 and has since become a leading international research department, with a large network of international collaborators, including partners in academia, government and industry as well as regulators. DCE publishes over 250 scientific publications annually (www.kea.au.dk/en/Publications.html).

PEOPLE

Almost 100 people from 10 different countries are currently affiliated with the DCE. Twelve international experts are affiliated with the department as visiting professors, adjunct professors or part-time professors.

EXPERTISE

Thanks to its multidisciplinary staff, DCE has decades of combined expertise in all major areas of clinical medicine, epidemiology, biostatistics, and research methodology.

DATA AND METHODS

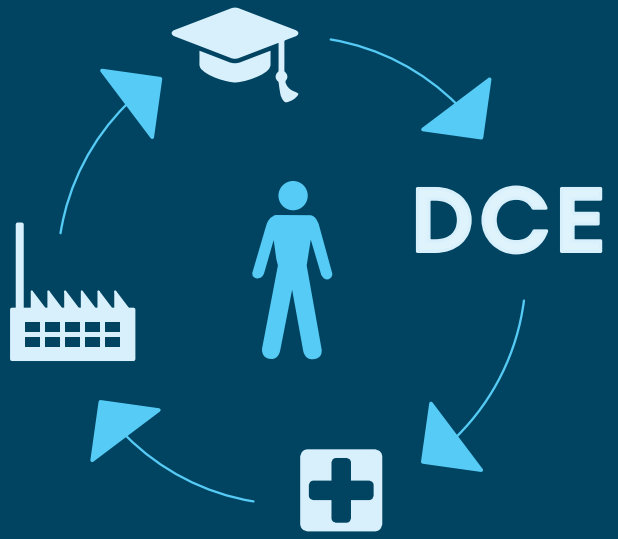
DCE researchers have long used information on biomarkers in their research, with examples including exploration of prognostic significance of cancer genotypes; investigating a biomarker-based response to cancer treatment; identifying biomarker-linked lifestyle factors in patients with diabetes; and using biomarker data to define complex algorithms for epidemiologic research.

Why collaborate with DCE?

Conducting research projects with DCE

Q: Who conducts the study?

A: Projects are research collaborations with regulators or partners from academia or industry. At a minimum, a project team includes an experienced epidemiologist, a biostatistician and a clinical consultant. Depending on the requirements of the specific study, the project team may also include an administrative assistant, a data manager, a research nurse, a laboratory technician, or a pathologist. All studies begin with a detailed protocol developed by the study team in collaboration with the sponsor.



Q: How long does it take to complete a project?

A: Project duration depends on the type of data required, the extent of the need for medical chart review and the nature of the required follow-up. A project based solely on secondary registry-based data (including routinely collected biomarker data, for example, from routine pathology or laboratory examinations) takes 3-12 months to complete, depending on the complexity of the analyses and the type of data needed.

Q: How will the study results be disseminated?

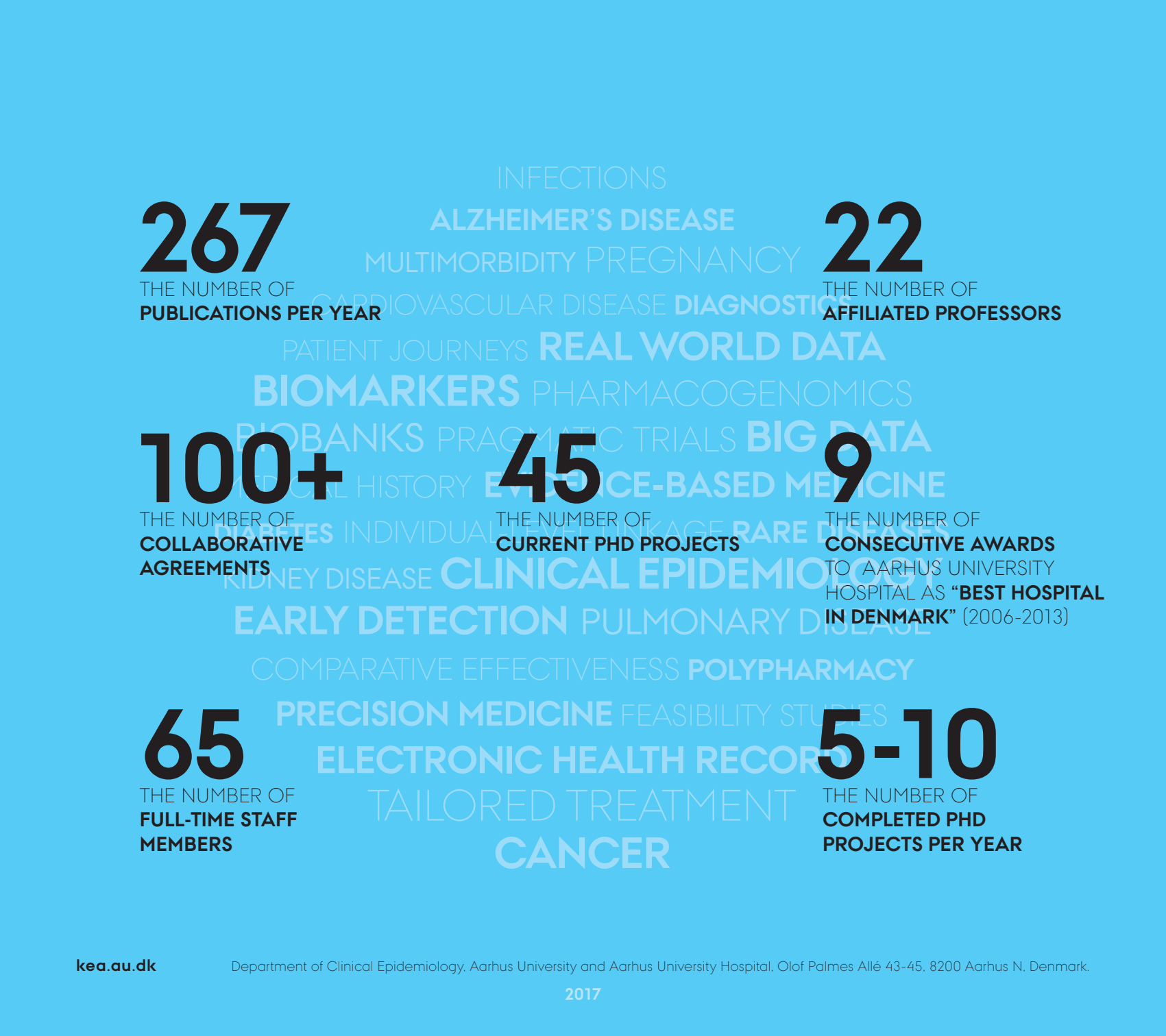
A: As an academic department, DCE has an ethical obligation to publish results of all research. It is expected that each research project will lead to one or several publications in peer-reviewed journals. DCE follows the authorship guidelines put forth by the International Committee of Medical Journal Editors.

Q: How do I initiate a new project with DCE?

A: Please submit your project inquiry to Professor Henrik Toft Sørensen, Head of Department (hts@clin.au.dk). We will then assess study feasibility, estimate initial patient counts, determine the need for a formal feasibility assessment and propose a project plan. We will also identify the need to include data from other countries and can coordinate multinational efforts.

Q: What about data protection and privacy?

A: All research at DCE is conducted in accordance with the applicable Danish legislation, specifically the Danish Act on Protecting Personal Data. Depending on the data needed for a project, DCE staff will obtain all permissions necessary to conduct the project.



267
THE NUMBER OF
PUBLICATIONS PER YEAR

22
THE NUMBER OF
AFFILIATED PROFESSORS

100+
THE NUMBER OF
COLLABORATIVE AGREEMENTS

45
THE NUMBER OF
CURRENT PHD PROJECTS

9
THE NUMBER OF
CONSECUTIVE AWARDS
TO AARHUS UNIVERSITY HOSPITAL AS **"BEST HOSPITAL IN DENMARK"** (2006-2013)

65
THE NUMBER OF
FULL-TIME STAFF MEMBERS

5-10
THE NUMBER OF
COMPLETED PHD PROJECTS PER YEAR

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