



**The Nordic Pilot project for
using a joint Nordic study
base:
Biomarkers for and
etiology of colon cancer**

Joakim Dillner

What is the Nordic advantage, really?

-Possibility to link nationwide, comprehensive registries on health data, heredity, sociodemographic factors, biospecimens etc

Cohorts with follow-up – an essential medical research infrastructure

- Cohort roots: samples and baseline data
- Follow-up for disease and cause of death – preferably for decades - is necessary to provide the "study base" that molecular research can be based on.
- Requires linkage of cohorts to comprehensive registers.
- To fully exploit cohorts for research, they need to be followed up and big biomedical data added to them!
- The resulting Study Base should be openly available for joint Nordic research
- Strategic development of a unique Nordic advantage!

What is at stake and what do we need?

- **Biomedicine and health is essential for development of society – comparable to fish & forest!**
- **The Nordic competitive advantage is the big, linkable biomedical data.**
- **We can not use aggregated or anonymous data: i) Registry follow-up is based on identifiable data (PIN) ii) Samples to be picked up must be identifiable.**
 - **But once retrieved data and samples are analysed coded, without research results being linked to any specific subject.**
- **Very few joint Nordic studies: Why?**

”Please be specific - Exactly what is the problem and exactly what is needed?”

- Essentially everyone wants to help – patients, politicians, lawmakers, experts et c
- But where are the bottlenecks, really?

Legislation on biotechnology in the Nordic countries – an overview 2014

10. Human biobanks

	Denmark	Finland	Iceland	Norway	Sweden
Law	No specific act on biobanking, i.e. the general legal framework set out in the Data Protection Act, the Health Act and the Act on Biomedical Research applies.	Biobank Act (688/2012)	Biobanks Act, No 110/2000 ⁴⁴ and Regulation No 1146/2010, on the storage and utilisation of biological samples in biobanks (English version not available).	Act relating to treatment biobanks (21.2.2003/12) Act on medical and health research (20.6.2008/44) Act on personal health data filing systems and the processing of personal health data (18.5.2001/24)	Act on biobanks in health care (23.5.2002/297) ⁴⁵
Scope of field (e.g. clinical/research/both)	n/a	<p>The aim of the Biobank Act is to support research where human biological samples are being used, foster transparent and open use of samples, and safeguard privacy and self-determination of the people whose samples are handled.</p> <p>The scope of application is storage and handling of human origin biological samples for <i>biobank research</i> that is defined as: "research that exploits the samples and related data that are being stored in a biobank and the aims of which are health promotion, understanding of disease mechanisms or development of products and practices to be used in the health care and cure".</p>	<p>The Biobanks Act applies to the collection of biological samples, and their keeping, handling, utilisation and storage in biobanks.</p> <p>The Act does not apply to temporary keeping of biological samples taken for purposes of clinical testing, treatment, or for specific scientific study, provided such samples are destroyed when the tests, treatment or research are completed. Temporary keeping means storage for up to five years, unless the National Bioethics Committee authorises a longer period of storage. Should the long-term preservation of such samples be desired, they are to be stored in a biobank.</p>	<p>The Act relating to treatment biobanks regulates the collection, storage, processing and destruction of human biological material that is part of a treatment biobank/diagnostic biobank.</p> <p>The Act on medical and health research regulates medical research on humans, human biological material, or health records.</p> <p>The aim of the Act on personal health data filing systems and the processing of personal health data is to contribute to information on and knowledge of the state of public health, causes of impaired health and illness trends for administration, quality assurance, planning and management purposes.</p>	<p>The Act applies to:</p> <ol style="list-style-type: none"> 1. Biobanks established in Sweden as part of a care provider's medical activities, irrespective of where the material is stored. 2. Tissue samples from a biobank that are released for storage and use on the premises of another care provider, an institution for research or diagnostics, a public research institution, a pharmaceutical company or other legal entity, and which are traceable to the person or persons from whom they originate. <p>Relevant parts of the Act apply to tissue samples taken and collected for transplant purposes in accordance with the Transplants Act (1995:831).</p> <p>The Act does not apply to specimens routinely collected in the course of medical care for analysis, and which are solely intended to form the basis of a diagnosis and the ongoing care and treatment of the donor, and which are not stored for a long period (normally 2 months).</p>

Generation and exploitation of Nordic big linkable biomedical data for medical research

- **We will identify and validate FAIR data and samples to build up national “ready-to-use” study bases with high quality.**
- **These study bases will be built for one disease endpoint at a time. They will contain data both on exposures and clinical data; and will contain samples taken both before, at and after diagnosis.**
- **We will combine genealogy, prospective cohorts and exposure assessments in several generations**
- **We will use the best available and useful domestic and international expertise and technologies to fulfill the best possible research purposes applied on the study bases.**

The Colon Cancer Pilot

- **Series of Nordic networking meetings: Colon cancer selected as pilot disease for joint Nordic studies.**
 - Sufficiently common to be important. Sufficiently uncommon to make studies in one country only too small.
- **Expected Result: Very large-scale Nordic study providing information from registries and biobanks, on the etiology and early diagnosis of a pilot disease**
- **Major purpose also to identify and report on the bottlenecks encountered when trying to do this.**

Ethical application (piloted by Sweden)

- **Very general in concept: "Biomarkers and etiology of colorectal cancer".**

-Specific hypotheses: Genomics, proteomics, transcriptomics, metabolomics et c. Waiving of consent applied for.

-Cohorts and registries to use: All biobanks registered at the Swedish National Board of Health and Welfare. All registries known to us.

-Ethical and legal arguments checked by ethicists and lawyers.

The permission has established that large-scale, joint Nordic research is allowed also with the present ethical/legal framework.

Some identified bottlenecks

- **No clear legal basis for general and infrastructural projects – only for “specific” research projects.**
 - **Collection of specific research projects added to the Nordic work plan already from the start. Caused significant delays.**
- **Scientists not used to asking for ethical and legal advice when preparing an ethical application: Defeatist attitudes.**
- **We had to file first in Sweden and based on the Swedish permission ask the other countries to file similar ethical applications.**
 - **Significant time delays.**
- **Possible solutions:**
 - **Scientific community: Learn to use ethicolegal advice and go for it if so advised!**
 - **Nordic Ethical Reviews?**

Registry linkages

- PINs on everyone who has been diagnosed with colon cancer.
- PINs on mothers, fathers, siblings, cousins.
- Hereditary risk of colon cancer determined: Analysis of samples from patients with high hereditary risk likely to be particularly informative.
- Asking for the PINs from the government (Cancer Registry): No problem (264000 PINs received).
- Asking for the relatives from the multigeneration registry at Statistics Sweden: Too much back and forth, waiting time et c. Tax office used instead (multiple linkages). When Statistics Sweden data did arrive, seemed more complete.
- Coded data sent for joint statistical analysis in Denmark. Strongly increased risk if relative with colon cancer:

Relative degree	Relative	Personal numbers	Count posts
1st	Child	200 154	205 007
1st	Mother	37 834	38 973
1st	Father	28 070	28 830
1st	Full sibling	22 011	22 509
2nd	Grandparent (mothers side)	4 744	4 811
2nd	Grandparent (fathers side)	3 302	3 345
2nd	Grandchildren	323 697	339 592
2nd	Aunties	593	599
2nd	Uncles	571	576
2nd	Nephews	21 792	22 389
2nd	Nieces	20 879	21 465
2nd	Half sibling	11 269	11 668
3rd	First cousin (mothers side)	678	691
3rd	First cousin (fathers side)	496	498
3rd	Great grandparents (mothers side)	287	287
3rd	Great grandparents (fathers side)	185	185
3rd	Great grandchildren	176 068	190 691

Some identified bottlenecks

- **Norway did not get permission from Statistics Norway to send coded data abroad (to Denmark).**
- **Change of administrative rules caused delays in Denmark and Finland.**
- **High demands on very specific protocol caused delays (before all Nordic scientists had agreed on exactly how to do the analyses).**
- **Possible solutions:**
 - **Advisable to not change the rules and regulations so often – takes time to learn**
 - **Should the Nordic countries really be classified as "abroad"? Legal change warranted?**

Sample requests

- Biobanks describe content in open catalogue. Pre-project contact to check that Open Access is honoured.
- But when we finally had permissions and filed the real sample request, things were different.....
- "Lip service open access"; First-come-first-serve with other projects filed since the pre-project contact; Scared; Just not used to sharing (no previous requests).
- Out of >30000 samples stored, "only" 8649 delivered.
- FAIR
- Technology development caused change in genomics – from "list of SNPs" to full genome sequencing. Completed for 50 cases/controls.

Nordic countries as key players for international research

- *If* we ensure that collaborating Nordic cohorts are similarly followed-up for disease endpoints et c using registry linkages – we will create a uniquely large and uniquely reliable study base for molecular research.

Why do we need Nordic collaboration?

- Routine linkages of biomedical data has important implications on development of best practises – notably on how to handle personal identifiers.
- It is mostly the Nordic countries who fully understand this issue – crucial to participate in the European development in this area.

Phase I & II

- Phase I:
 - Multigeneration linkages: Heritability estimates. PIN retained - Samples can be identified.
 - Cohorts linked to registry data: DNA from both all colon cancer patients (>8000 patients) and patients with strong heredity retrieved. Large SNP array + Whole Genome Sequencing.

Phase I & II

- Phase II: Clinical studies
 - Hospital-based patient cohorts identified.
 - Joint Nordic research portfolio under development: Metagenomics, Metabolomics – in relation to treatment and clinical outcome.
 - Laboratory-based information.

Summary

- Formalities are laborious – but, joint Nordic research on big biomedical data
 - on all registries/biobanks in a country
 - for quite broad hypotheses

is possible and allowed also with the present ethical/legal framework.

- Big Nordic Biomedical Database is taking shape.

Issues *within* the scientific community very important.

- *Genuine will to share both data and samples (Open Access), also across country boundaries in the Nordic countries*
- *Similar way of working (preferably disease-oriented with continuous adding of new data to cohorts)*

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