Lessons learnt from Nordic cooperation in biobank-based research

A Nordic joint Biobank & Registry-based Study on Colorectal Cancer (The BBMRI_Nordic_Pilot)

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Biobanks with follow-up – an essential infrastructure for cancer research

- **Biobanking 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 biobanks to comprehensive registers.**
- **Biobanking is <u>not</u> just about not having to collect samples – it is about *not having to wait for the outcomes*.**
- **Strategic devlopmen of a unique Nordic advantage.**

Generation and exploitation of Nordic Biobank Materials for medical research

- **Aim: To identify and validate samples and data from participating biobanks to build up national "ready-to-use" biobank-based 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 BBMRI joint Nordic project on biobank-based research

- **Is a research project - it is *not* a new biobank**
- **The national biobank platforms will:**
  - **Systematically identify i) cases and controls and ii) accessory data from Nordic biobanks using registry linkages using PINs.**
  - **File applications for ethical permission & biobank withdrawals.**
- **This ”ready-to-use” infrastructure will then be made openly available to Nordic scientists.**

From the biobank perspective

- **A Nordic collaborative research project will drive real-life standardisation & harmonisation in the Nordic countries.**
- **High –profile project: to show that the Nordic countries *can indeed collaborate* on biobank-based sciences.**
- **Optimises the scientific output from biobanks by facilitation of more large-scale sciences.**

Work flow

- BBMRI_Nordic coordinators search their respective countries for a) samples and data and b) interested PIs (scientific champions)
- First ethical permission for registry linkages and sample analyses for the first set of hypotheses.
- BBMRI_Nordic defines a study base with Nordic data and samples, validated for quality & comparability
- Cancer endpoints in family added to database as hereditary risk factor
- Additional hypotheses can be added as “Add-on”-studies (supplement to Ethical permission).

Some identified bottlenecks

- **New policy on biobank & registry use in Sweden: General and infrastructural projects not allowed – only ”specific” projects.**
    - **Solution: Collection of specific projects added to the Nordic work plan already from the start. Caused significant delays.**
- **The principle that biobanks should be openly accessible is not as widely accepted as we thought.**
- **Some colon cancer experts say no to collaboration.**
- **Different ways of working for the biobanks in different countries.**
    - **Swedish biobank-based research typically based on one basic Ethical permission per disease, to which new hypotheses are added as ”add-on” ethical permissions.**
    - **Other countries use a ”fragmented” approach with each hypothesis separated from others, even on the same disease.**

Disease-orientation or Project-orientation?

- **Disease-orientation:**
  - **Biobank in the center.**
  - **Research data on disease archived at the biobank**
  - **Enables investigating effect of confounding (adjusting possible etiologic exposures for each other) and added value of biomarkers (adjusting predictive ability of new biomarker for previously known biomarkers).**
  - **Open access to both samples and research data is nowadays requirement from both funders and journals – provides possibility for real re-use.**
  - **No legal obstacles for large-scale data (except that interlinkage requires new permission).**

Name of Biobank	Country	Number of colorectal cancer cases	Type of sample
Umeå Maternity Cohort	Sweden	223	Serum
Northern Sweden Health and Disease Study	Sweden	969	Plasma
Malmö Microbiology Biobank	Sweden	5 331	Serum
Malmö Diet and Cancer	Sweden	895	Plasma, serum, erythrocytes, granulocytes, buffy coat and mononuclear leukocytes
Malmö Preventive Project	Sweden	1 046	Plasma and serum
Biobank 242, dept. of surgery, SU/Östra, Göteborg	Sweden	4 163	Fresh-frozen + paraffin-embedded tumor and mucosa biopsies; plasma, serum, buffy coat
Helsinki Heart Study	Finland	380	Serum
Finnish maternity Cohort	Finland	800	Serum
ABTC (Alpha-Tocopherol-Beta-Carotene Cancer Prevention Study	Finland	630	Serum and whole blood
Finnish mobile clinic health examination survey	Finland	796	Blood
FINRISK	Finland	94	Serum
JANUS Project	Norway	5 114	Serum
Copenhagen Hospital Biobank	Denmark	2454	Whole blood
Greenland Biobank	Greenland	58	Serum, plasma, buffy coat, filter paper
Icelandic heart preventive clinic	Iceland	707	Serum
Icelandic maternity cohort	Iceland	67	Serum
The Biobank of the Pathology Department of Landspitalinn-University Hospital.	Iceland	3 000 to 3 500	Fresh frozen biopsies and paraffin-embedded samples
Total		~27 000	

Country	Name of research project	PI responsible for the project	Status
Sweden	Probiotics for prevention of CRC	Yvonne Wettergren, University of Gothenburg	Project summary is written
Sweden	Folate and CRC	Jörn Schneede, Umeå University	Project summary is written
Sweden	Protein biomarkers of CRC	Joakim Dillner, Karolinska Institute, Stockholm	Project summary is written
Sweden	Validation of a technique determining the lymph node status of CRC patients	Marie-Louise and Sten Hammarström, Umeå University	Project summary is written
Sweden	Evaluation of existing Biomarkers of CRC	Christina Hall, Fujirebio, Göteborg	Project in planning phase
Sweden	Recombinant Antibody Microarrays for Oncoproteomics	Christer Wingren, Lund University	Project in planning phase
Finland	Genotyping of CRC risk SNPs	Lauri Aaltonen, University of Helsinki	Project summary is written
Denmark	Molecular profiling of tumors, depending on the site in the colon	Tine Jess, Statens Serum Institute, Copenhagen	Project in planning phase

Ethical application

- **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.

-Biobanks to use: All biobanks registered at the Swedish National Board of Health and Welfare.

-Ethical and legal arguments checked by BBMRI.se ethicists and lawyers.

Ethical application: Response

- **Please be somewhat more specific on the analyses.**
- **Waiving of consent is fine, but please include an ambitious ”communication plan” for conveying information to the public via media, internet, patient organisations et c.**

Very sensible!

With some more specifics on analyses + Communication Plan = Ethical approval.

Example of ”specific” analyses description

- **Eftersom utvecklingen sker mycket fort inom de flesta tekniska analys-områden så kan det tänkas att de nedan beskrivna metoderna kan behöva ersättas med nyare, bättre tekniker. De tekniker som beskrivs nedan är de bästa kända i dagsläget.**
- **-Genomik (screening för en sorts genetisk variation, så kallad single nucleotide polymorphisms (SNPs) samt helgenomssekvensering med nästa generations DNA-sekvensering):**
- **För helgenomssekvensering samt även screening för SNPs: 454 GS FLX Titanium från Roche, HiSeq och MiSeq från Illumina samt Ion Proton från Life Sciences För genotypning av olika SNPs avses även Illuminas Infinium assay användas. DNA-metylering: kommer att mätas med Illuminas ”whole genome methylation array” samt EpiTect Methyl qPCR Arrays från Qiagen.**

Genotyping of Colorectal cancer risk SNPs

Principal Investigator: Lauri Aaltonen, Professor

Department of Medical Genetics, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland

Genotyping >20 CRC risk SNPs in sufficient number of cases and controls should shed light on possible additive effects of risk genotypes and other risk factors.

Comparison with linkages on heredity useful to investigate if the investigated SNPs explain the hereditary risk of CRC.

Significant deliverable of project

- **We have established that large-scale, joint Nordic biobank-based research**
  - **on all biobanks in a country**
  - **for quite broad hypotheses**

  is allowed also with the present ethical/legal framework.

  Ethical application with the same wording is now being filed in all the Nordic countries.

Summary

- **Ethical/legal/administrative issues found to be major bottleneck for rapid progress.**
- **Joint and broad Nordic biobank-based studies are possible, also within the existing ethicolegal framework.**
- **Issues *within* the scientific community very important.**
  - ***Genuine will to share both data and samples (Open Access)***
  - ***Similar way of working required (preferably disease-oriented with continuous adding of new data to the biobank cohorts)***
  - ***Genuine will to collaborate outside the home university***