Lessons learned from Nordic research collaboration – The Nordic colon cancer project

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What is the Nordic advantage, really?

- Possibility to link biobanks to nationwide, comprehensive registries on health data, heredity, sociodemographic factors et cetera.
Biobanks with follow-up – an essential medical research infrastructure

- 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 not just about not having to collect samples – it is about not having to wait for the outcomes.
  - To fully exploit biobanks for research, they need to be followed up!
- Strategic development of a unique Nordic advantage.
Biobanks with follow-up – an essential infrastructure for medical research

- Molecular research is based on biospecimens.

- Etiological research
  - Search for explanations to differences in disease occurrence.
    - Causal exposures may have occurred long ago or may change over time.

- Clinical research
  - Search for biomarkers of response to treatment
    - Clinical outcome must be known.

- Prevention research
  - Search for early diagnosis methods/screening tests
    - Future diagnoses must be known.
Registry infrastructure in the Nordic countries

**Personal Identification Number (PIN)**
- A unique number given at birth or at immigration

**Health care**
- It is mandatory to report health events to nationwide registers
- The health care system uses the PIN

**Registries**
- Collect health data for e.g. cancer, hospitalisations and birth data.
- The registries use the PIN

**Biobanks**
- Population-based biobanking cohorts/systems in health care, e.g. cytology biobanks.
- The biobanks use the PIN
Nordic coordination of biobanks required: The user perspective

1. Scientist who would like to use samples and data for nationwide study.

2. Education on the science of biobanking, finding information on biobanks, what they contain, their quality et c.

3. Dialogue with a) biobanks on optimal study design & analysis. b) analysis platforms on sample analysis

4. Applications to multiple biobanks.

5. Application to Ethical Review Board.

6. Application for registry linkages.

7. Registry linkages, selection of cases and controls.

8. Case verification process.

9. Sample retrieval and sample handling logistics.

10. Validation of quality and comparability of samples from different biobanks

11. Accessory data retrieval a) from biobank databases b) from registry linkages.

12. Validation of quality and comparability of accessory data.

13. IF data and samples are found to be sufficiently comparable and high quality - analyse the samples and the data.

Typical time from idea to sample/data analysis: 2-4 years.
Scientific coordination required: The biobank perspective

- 1. Application to use samples and data on a particular disease received from a single scientist working on a single hypothesis.
- 2. Extensive biobank personnel time required for education, dialogue, registry linkages, data and sample retrievals.
- Shortly afterwards a new application from another single scientist working on a single hypothesis on same disease is received.
- Entire process needs to be repeated again. Waste of time and samples. Limited scientific impact by multiple small projects.
- Questionable scientific validity – different hypotheses can not be compared unless included in the same study (control for confounding). Limited scientific impact of non-coordinated studies threatens the long-term sustainability of the biobanks.
Scientific coordination required: The scientific perspective

- In research on etiology, all risk factors should be studied.
- Necessary for evaluation of whether factors associated to disease are mere secondary associations (confounding) or true risk factors.
- **Exactly the same** study base with samples and data should be used.

- In predictive sciences (e.g. biomarkers for diagnosis or therapy selection) all biomarkers and predictive factors should be studied.
- Necessary for evaluation of whether a new biomarker associated to disease or successful therapy contributes anything over and above what can already be predicted with known markers.
- **Exactly the same** study base with samples and data should be used.
Exploiting biobank cohorts using coordination by disease endpoint

- **Study bases with samples and data defined by registry linkages. All research data obtained systematically added to study base.**
- **Requests for samples and data received are coordinated with other requests and prior projects on the same disease.**
- **Similar systems already in use for several decades by the many successful Nordic biobanks.**
BBMRI_Nordic (Nordic Biobank Network)
NordForsk-funded Collaborative Network between the National Biobanking Infrastructures in the Nordic Countries
Generation and exploitation of Nordic Biobank materials for medical research

- We will 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.
BBMRI Nordic_Pilot: Colon Cancer

- Colon cancer selected as pilot disease
- Expected Result: Very large-scale Nordic study providing information from registries and biobanks, on the etiology and early diagnosis of a pilot disease
- If successful, concept could be copied to enable joint Nordic studies on any disease
The BBMRI_Nordic pilot project on joint 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.
Some bottlenecks and problems

Ethical permission: Widespread defeatism among scientists. But ERBs were supportive.

-Application first piloted in Sweden, then filed in the other countries.

Government Agencies: Supportive (e.g.: Swedish National Board of Health & Welfare delivered data on 234000 colon cancer patients).

Biobanks: Not as Open Access as stated. In the end, samples from "only" 10,000 colorectal cancer patients (+ controls) were provided.
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.

-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.

• The permission has established that large-scale, joint Nordic biobank-based 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" projects.
  - Solution: Collection of specific projects added to the Nordic work plan already from the start. Caused significant delays.

- The Open Access principle was not as widely accepted as we thought.

- Some scientific experts say no to collaboration.

- Different ways of working for the biobanks in different countries.
  - Most biobank-based research typically based on one basic Ethical permission per disease, to which new hypotheses are added as "add-on" ethical permissions.
  - Other biobanks 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).
Nordic biobanks as key players for international research

- If we ensure that collaborating Nordic biobank 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.

- Health and biomedical research: An issue of national strategic importance.
Opportunities for Nordic biobank collaboration

- Routine linkages of biobanks to registries 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.
Opportunities for Nordic biobank collaboration

- *If* collaborating Nordic biobanks can be similarly followed-up and have the study bases similarly presented to the scientific community, we could provide striking examples on how international joint use of several biobanks can be used for large-scale research.

- *Help to focus on the infrastructural work on how to best provide a basis for excellent science.*
Summary, I

- Formalities were laborious – but the BBMRI_Nordic Colon Cancer study has established that large-scale, joint Nordic biobank-based research
  - on all biobanks in a country
  - for quite broad hypotheses

is possible and allowed also with the present ethical/legal 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*
Summary, II: Ethics

• Comparison of rules on Ethical permission: Very similar rules all over Europe – Decisions on e.g. consent procedures rest with the Ethical Review Boards.

• Bottlenecks on rules:

  • ERB decisions only valid in one country.
  
    • ERBs may make different decisions – can make joint research impossible.
  
    • Joint research has the speed of the slowest participating country.

• Rules against sending samples abroad: Sweden, Norway and the People’s Republic of China.

• Major problems in scientist attitudes: Defeatism; Lack of skills in clearly arguing their case (no tradition in asking for help in ethical/legal matters); Modern research principles still not widely accepted (Open Science/Open Access/Large-scale international science).
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• Very large number of biobank managers and interested scientists in all the Nordic countries