The Swedish National Biobank Program is a joint national program of the two Swedish initiatives on functional genomics, Swegene and Wallenberg Consortium North, supported by the Wallenberg Foundation and by the major universities of Sweden.
The National Biobank Program has been running from 2002-2005, with an overall budget of more than 51 million Swedish kronor. Coordinator is professor Joakim Dillner.

The program works through strategic measures directed towards a network of Swedish biobanks and registries, with the aims to:
-Increase the quality, usefulness, efficiency and accessibility of Swedish biobanks for health-related research as well as for clinical care and treatment.
-Improve the systems and standards for ensuring protection of the integrity of individual donors, including promoting ethical awareness.

A national program with comprehensive participation of major Swedish Biobanks

The major parts of the program are:
1. **Population-based research biobanks** with **comprehensive collection of phenotypic and environmental information** as well as biobanking of at least **buffy coat, plasma and erythrocytes** stored at minus 80 C or lower.
The four participating research cohort biobanks (Umeå Medical Biobank, Malmö Diet & Cancer, Malmö Preventive Medicine, Twin Gene Biobank) together contain blood samples from >185.000 sampling occasions.
Because major participating biobanks were established >20 years ago, the amount of prospectively occurring endpoints of disease in the cohorts is more than sufficient for most study designs.

PROSPECTIVE CANCER CASES	Medical Biobank Umeå	Northern Sweden Maternity Cohort	Malmö Micro-biology Cohort	Malmö Diet &Cancer; Preventive Medicine	SUM
Colon	253	34	425	548	1103
Lung	148	22	539	938	1341
Breast	996	397	892	1196	3380
Cervix uteri	117	119	211	329	749
Prostate	557	-	736	1856	2199
Kidney	650	10	179	177	1016
Melanoma	209	67	363	371	1010
Skin	52	4	963	434	1453
Any Cancer	4524	1022	7415	6859	19820

Number of prospectively occurring endpoints of cancer and some forms of cancer in some biobanks

The samples in the prospective research biobanks are aliquoted into color-coded tubes (buffy coat, EDTA-plasma, heparin-plasma and so on).

2. Pathology biobanks.
Participating pathology biobanks contain >10 million conventional pathology specimens. There are also about 24.000 fresh-frozen specimens that have been stored at minus 80.

3. Microbiological serology banks, containing >1.7 million serum or plasma samples and expanding by 120.000 samples/year.

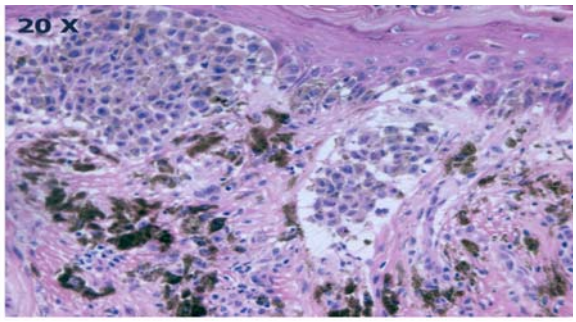
Accessibility and Quality: All participating biobanks have committed themselves to work using **common quality standards** and to provide **access to samples** after prioritisation on scientific grounds only. For more information on these biobanks and how to apply for access, please visit
www.biobanks.se/swedish%20biobanks.html

The freezer facility of the Medical Biobank in Umeå

*Prospective collection of biobank samples

The population-based research cohorts have, with financing from the National Biobank Program, during 2002-2004 collected an additional **40.000 blood samples,** with the same comprehensive collection of associated **phenotypic and environmental information.**

The tissue biobanks have collected **about 6.000 fresh-frozen tissue samples**. Technology development that gives equal morphological quality for histopathological diagnosis using frozen tissue (avoiding the use of formalin) has improved the possibilities to collect consecutive series of fresh-frozen tissue.



Fresh-frozen tissue section used for routine histopathology.

*Supplying biobank samples for research

The participating biobanks have been subsidized to increase output of delivering samples and accessory data for studies.

The Malmö Diet & Cancer and Preventive Medicine biobanks supplied 56 different research projects with 56.000 samples (36.622 extracted DNA and 19.299 plasma or serum samples). The Uppsala Frozen Tissue Biobank supplied samples to 17 research projects.

*Facilities for sample handling and analysis

The National Tissue Microarray Center

is equipped with a fully computerized robotic tissue arrayer. The center has constructed a series of high quality tissue arrays with several thousands of specific tumors as well as tissue from other diseases, that are now accessible to the scientific community. The associated database contains the clinical information from the medical charts. Our breast and colon cancer arrays are also linked to prediagnostic blood samples and questionnaire data. Currently available arrays are listed at www.biobanks.se. The center is also offering “for service” construction of tissue arrays from paraffin-embedded materials provided by customers.

Robotic Dispensing facility

The large Medical Biobank in Umeå has been equipped with a robotic dispensing and aliquoting facility that has markedly enhanced the sample delivery output capacity.

Regional Biobanking Facilities

The program has subsidized the continued development of Regional Biobanking Facilities (in Umeå, Uppsala, Karolinska and Malmö) that provide clinical researchers with for-service quality-assured, standardised handling and storage of biobank samples and associated data.

DNA extraction facilities

The program has financed two facilities, one at Lund University in Malmö and one at Karolinska Institute in Stockholm. Both are equipped with robotic DNA extraction systems.
An important deliverable of the program is the Malmö Diet & Cancer Cohort **"DNA array"**- DNA from the buffy coat samples of a population-based research cohort of 32.000 subjects has been extracted and arrayed in a bar-coded 96-well format, linked to a robotic pick-up system. During 4 years of operation, the Malmö Regional Biobanking and DNA Extraction Facility performed 53373 DNA extractions, retrieved 13029 samples from the DNA arrays and performed for-service whole genome amplification of 220 samples.

The bar code of a "DNA array" being checked before storage.

*National Quality Standards

The first version of a common Quality Assurance manual for biobanking, termed "Good Biobanking Practise" was produced in 2002 and has been implemented in all participating biobanks. In april 2004, a modified version of the Quality Assurance manual was recommended by the Swedish County Council Association for common use in all biobanks throughout the Swedish healthcare system.

The program has also developed common Quality Standards for evaluating different methods of handling samples with regards to DNA, RNA and protein integrity and a series of recommended Standard Operating Procedures for sample handling.

*Ethics and law

An active research group within bioethics and law has arranged a series of seminars, books, scientific articles and a website (www.bioethics.uu.se/biobanker) to promote knowledge about the legal and ethical rules surrounding biobanks, stimulate ethical debate and assist in the development of practical solutions that conform to legal and ethical standards.

*Education and networking

Several postgraduate courses on biobanking, registry linkages, sample handling and analyses have been given. A website for education in statistical genetics has been launched (www.meb.ki.se/genestat/genestat.htm). Planning of joint scientific biobank-based studies has also been supported.

*Regional Biobank Registries

Regionalt biobanksregister
för Södra sjukvårdsregionen

The first, pilot Regional Biobank Registry (RBR) with mandatory registration of all samples stored within the healthcare system in a healthcare region was established in Southern Sweden in 2003, financed jointly by the National Biobank program and the regional county councils. Most health care regions in Sweden have followed and are now also building RBRs.
The RBRs are providing a **world-unique** opportunity for complete **overview** regarding exactly which samples that have actually been stored and would be available for research.
The RBR is administrating the **consent management**, providing a practical option for retraction of informed consent for any and all storage and for any and all research.

Finally, the RBR is providing a **pseudonymisation service ("Third party code-keeping system")** that makes it possible to perform research without ever linking research data to individuals: Only the RBR (not the researchers) have access to the code.

Broad consent to research is administrated throughout the health-care system.

A standardised informed consent is today given to all patients donating samples donating samples in the Swedish health-care system (about 3 million consents per year). The RBR is co-ordinating the system, monitors the quality and ensures that no samples are stored or used against the wish of the donor. So far, only about 0.2% of patients have declined storage or told that the stored samples should not be used for research.

Till dig som lämnar prov

Som patient behöver du ofta lämna prover, till exempel blodprov eller vävnadsprov. Prover tas också vid de hälsokontroller som landstinget erbjuder. Vissa prover sparas rutinmässigt i en så kallad biobank. En biobank är en samling prover – blodprov, cellprov eller andra vävnadsprover – som tas i vården och sparas längre tid än två månader och som kan härledas till en viss person.

Mer information

Vill du ha mer information kan du fråga din läkare eller vända dig till Regionalt biobanksregister, Universitetssjukhuset i Lund, 221 85 Lund.

Excerpt of the standardised informed consent administered throughout Swedish health care- from maternity care, to cervical screening, surgery, pathology and autopsy.

*A Complete Swedish Multigeneration Registry

The Swedish Multigeneration Registry contains information on first-degree relatives to subjects born in Sweden from 1932 and onwards. When the registry was transferred to the Tax Authorities in 1991, information on dead index subjects was not systematically computerized. This has severely hampered the study of genetics of lethal diseases, such as cancer, in Sweden. The National Biobank Program has therefore financed the manual retrieval of the missing information from paper files, an enormous task that was finally completed in 2004.

*Scientific achievements

The program participants have produced well over 200 scientific publications. Complete listings are available in the annual reports posted on www.biobanks.se. Selected findings:

The major research biobanks in Malmö and Umeå that had their original focus on diet and cancer have continued to produce high impact findings on this subject:

van Gils CH, Peeters PH, Bueno-de-Mesquita HB et al. Consumption of vegetables and fruits and risk of breast cancer. JAMA. 2005 293:183-93.

Bingham SA, Day NE, Luben R et al Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet. 2003;361:1496-501

Discovery of molecular methods for early detection of rheumatoid arthiritis that are so powerful that intervention has become a realistic option: Berglin E, Padyukov L, Sundin U, Hallmans G, Stenlund H, Van Venrooij WJ, Klareskog L, Dahlqvist SR. A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis. Arthritis Res Ther. 2004;6: 303-8.

The successful elucidation of the role of infections in chronic diseases has been continued, with important leads detected in multiple sclerosis: Sundstrom P, Juto P, Wadell G, Hallmans G, Svenningsson A, Nystrom L, Dillner J, Forsgren L. An altered immune response to Epstein-Barr virus in multiple sclerosis: a prospective study. Neurology. 2004;62:2277-82.

The tissue microarray center has enabled a rapid discovery of new molecular markers of treatment response and/or prognosis in cancer: Stendahl M, Kronblad A, Ryden L, Emdin S, Bengtsson NO, Landberg G. Cyclin D1 overexpression is a negative predictive factor for tamoxifen response in postmenopausal breast cancer patients. Br J Cancer. 2004 90:1942-8.

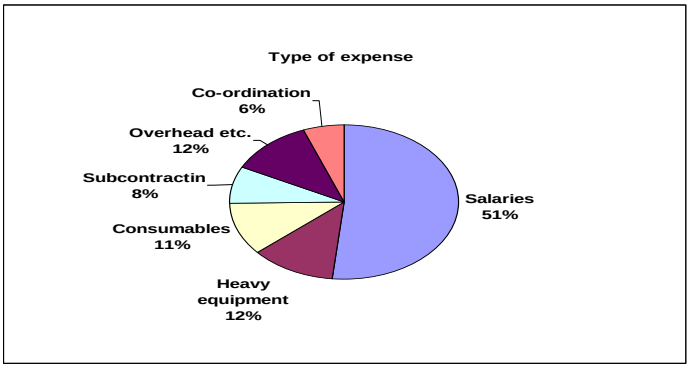
The work on quality and usefulness of different types of samples has established that archival plasma samples are useful for large-scale genotyping studies: Sjoholm MI, Hoffmann G, Lindgren S, Dillner J, Carlson J. Comparison of archival plasma and formalin-fixed paraffin-embedded tissue for genotyping in hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev. 2005 14:251-5.

The large number of scientific articles on law and ethics of biobanking has significantly

advanced the practical standards of biobanking and biobank-based research:
Hansson, M.G & Levin, M.: Biobanks as Resources for Health, Uppsala University, 2003 (ISBN 91-506-1659-6)

*Use of funds

Most of the funds have been used for salaries for scientists and technical personnell. During the course of the program, 46 individuals have being employed.



Swegene and WCN have shared the expenses at a 40%/60% split. As it has been a national program, the use of funds by university has not followed the expense sharing exactly.

	Total Expenses	Percent
Umeå	9 452 065	18,4%
Karolinska	16 907 812	32,9%
Uppsala	7 642 298	14,9%
Lund	17 233 009	33,5%
Gothenburg	226 175	0,4%
Sum	**51 461 360**	

*Program Principal Investigators in 2005

Node	Node PI
Umeå, Medical Biobank	**Göran Hallmans**
Uppsala, Ethics	**Mats G. Hansson**
Uppsala, Pathology	**Johan Botling**
Karolinska, Pathology	**Monica Niste´r Bertil Hamberger**
Karolinska, Twin Gene & KI Biobank	**Ulf de Faire Gunnel Tybring**
Karolinska, Multigeneration Registry	**Anders Ekbom**
Malmö Biobanks & Biobanking Facilities	**Göran Berglund Joyce Carlson**
Tissue Array Center	**Göran Landberg**
Regional Biobank Registry	**Thor Alvegård**
National Coordination	**Joakim Dillner**

*Summary

The National Biobanking Program has established nationwide collaboration and common biobanking standards on quality, access and protection of integrity.
The resources have been expanded by continued prospective collection of samples and data and important bottlenecks in sample purification, sample retrieval, sample arraying and data annotation have been remedied.
The development of uniform consent management, comprehensive sample overview and quality standards for health care-related biobanking has provided a world-unique opportunity for providing Sweden a decisive advantage in molecular clinically oriented research.
Significant advances in expanding the knowledge-base for better health have already been achieved and it is hoped that a solid foundation for continued biobank building and continued health-related biobank-based research has been obtained.

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