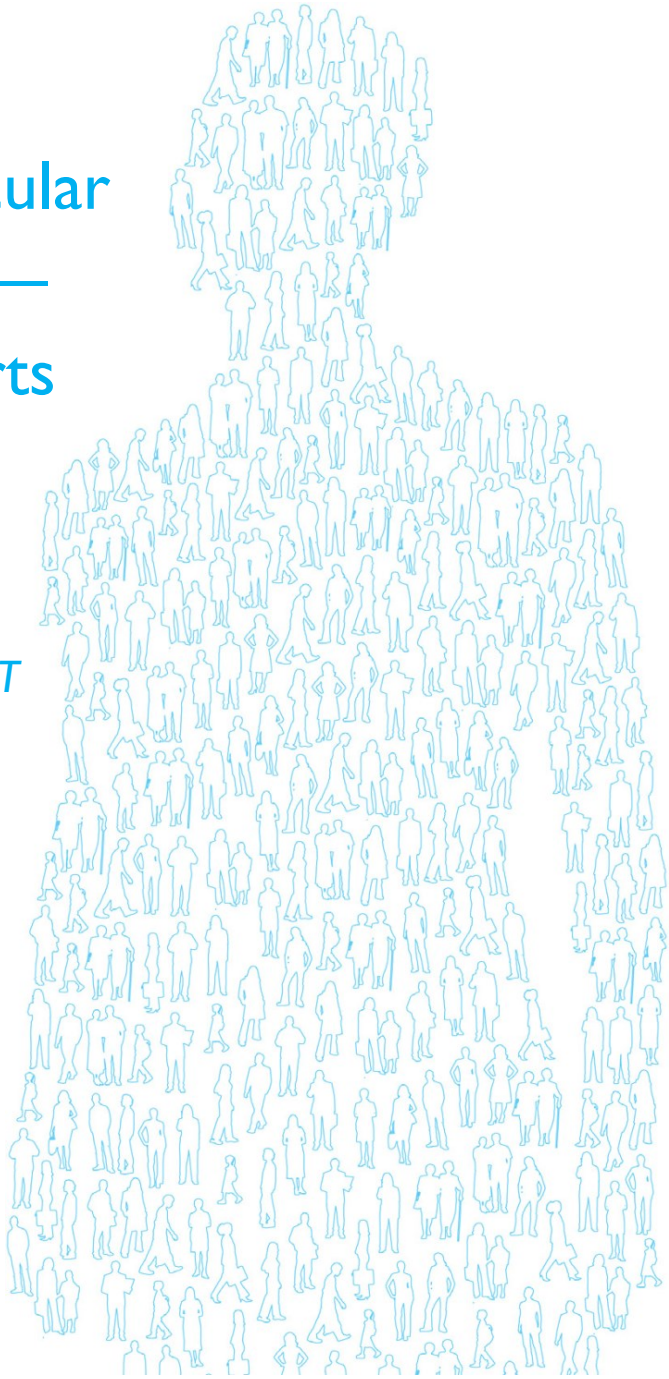
bbmri-lpc

BBMRI – Large Prospective Cohorts

Biobanking and Biomolecular Research Infrastructure — Large Prospective Cohorts (BBMRI-LPC)

FINAL PUBLISHABLE SUMMARY REPORT



The BBMRI-LPC Consortium was supported through funds from the European Commission Seventh Framework Programme; FP7-Infra-2012-1.1.9.; Grant Agreement No.: 313010;
Project duration: 1/2/2013-31/10/2017

4.1 Final publishable summary report

1.1. Executive summary

Samples with related data in large prospective cohort collections represent invaluable resources for present and future health research with a fundamental role in identification of etiological risk factors and biomarkers for diseases. To enable reliable analysis, prospective cohorts need to be large enough to accrue sufficient numbers of incident disease cases during follow-up. Consortium-based cohort studies are therefore instrumental in enabling the study of less common disease endpoints and highlight the great importance of collaborative cohort research in Europe.

Efficient sharing and pooling of samples and data from several different sources represents a central pre-requisite for advances in biomedical science, where the European Union (EU) is well-positioned to assume a pivotal role. This aim is counteracted, however, by the present scattered access governance structures where legal and ethical frameworks across national borders prevent effective sharing. Practical solutions are urgently needed for streamlined and harmonized governance of access in collaborative projects. This would optimize the scientific value and use of the available research resources, which has been a central aim of the present project.

Biobanking and Biomolecular Research Infrastructure — Large Prospective Cohorts (BBMRI-LPC) has brought together 20 large prospective cohort studies from 10 countries and two EU-wide multinational cohort networks, with a key objective of promoting collaborative transnational research on prospective cohorts and to analyze gaps in need of solution. By improving harmonization, and providing solutions for transnational access and networking, BBMRI-LPC aimed to increase utilization of large sample collections for research on human health. These objectives have been successfully met. Three scientific calls were organized to offer European investigators the opportunity to gain free of charge transnational access to the bio-specimens and data available in participating cohorts. In total, 24 research proposals were received, of which 11 high-quality projects were granted financial support for access to multiple prospective cohorts within BBMRI-LPC. The costs for downstream analyses were covered by the applicants with some limited funds made available from BBMRI-LPC in order to generate specific types of omics data.

The access process in individual access projects was carefully monitored. A number of areas were identified where infrastructural developments could improve access to large prospective cohorts in Europe. As the experience and knowledge obtained during the course of BBMRI-LPC is envisaged as benefitting the entire biobanking and medical research communities, best efforts have been made to document and disseminate the information acquired and provide recommendations for harmonized, improved access to biobanks. The BBMRI-LPC experience will help BBMRI-ERIC (Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium) in its aim of facilitating access and encouraging collaborative transnational research projects. Accordingly, several concepts and solutions developed during BBMRI-LPC are now being sustainably integrated within the BBMRI-ERIC Work Plan.

Besides achieving its primary aim of promoting access, BBMRI-LPC has also reached other central objectives. Through its versatile research activities, BBMRI-LPC has contributed to major advances in evidence-based research on biobank procedures and operations, as well as in development of advanced technologies for protein analysis based on antibody-DNA conjugates and protein microarrays. Other major achievements of the project include upgrading the value of selected samples stored in biobanks through omics analyses; actively contributing to the ethical and legal aspects of biobanking; actively contributing to structuring and harmonization of the biobanking networks; and monitoring existing public-private collaborations, while facilitating new ones.

By charting opportunities and pitfalls of transnational sharing of samples and data, together with the production of high-quality research results and other project activities, BBMRI-LPC has had a considerable positive impact benefitting epidemiological, clinical and therapeutic research. The knowledge obtained during the project will be of high general value for the field and will contribute strongly to future sample and data access procedures.

1.2 Summary description of project context and objectives

1.2.1 Project context

Population-based cohort studies have a fundamental role in identification of etiological risk factors and biomarkers for disease. In contrast to other study designs (e.g. case-control studies), prospective studies are not affected by recall or other biases as the risk factors are measured prior to the onset of the targeted disease outcomes. In large prospective cohort studies, research participants are recruited and followed over a long time, often for decades. Upon recruitment, the study participants (most of them healthy at baseline) typically undergo a detailed set of medical examinations and anthropometric measurements, complete a questionnaire or interview covering various health, diet and lifestyle factors, as well as providing bio-samples for future analyses, most commonly as blood (serum, plasma, DNA from peripheral blood mononuclear cells), urine or saliva. The participants are subsequently followed over time to identify disease outcomes or death using various follow-up strategies.

A high number of large prospective cohort studies have been carried out across Europe over recent decades. These cohorts constitute a unique mixture of '*mature cohorts*' with an extensive follow-up period of several decades, and '*contemporary cohorts*' with more recent and often enriched exposure information. Some of these (e.g. UK Biobank and the EPIC cohort) have recruited hundreds of thousands of study participants, representing major investments of public funding as well as time and effort from study participants and researchers. With their stored samples and extensive exposure information, the large prospective cohort studies represent an invaluable resource for present and future health research.

To enable analysis of diseases in a reliable manner, prospective cohorts need to be large enough to accrue sufficient numbers of incident disease cases during the follow-up period. Studying rare or moderately common endpoints in a single prospective cohort is often challenging and in many cases pooling resources across multiple cohorts from several countries is required to assemble sufficient sample size for answering important research questions. While consortium-based cohort studies are instrumental to study less common disease endpoints, such multinational research projects, however, are often challenged by sample and data sharing difficulties due to limited resources and heterogeneous country- and cohort-wise access procedures. Multiple time-consuming processes specified in national legislations and local rules have to be complied with, which may markedly expand the time needed before the actual research can commence. This heterogeneity is not only observed across regions (e.g. the European Union), but even between different cohorts or biobanks within a single country. Regrettably, the burden of current fragmentation falls on the scientists and laboriousness of transnational access tends to impede progress of the science itself.

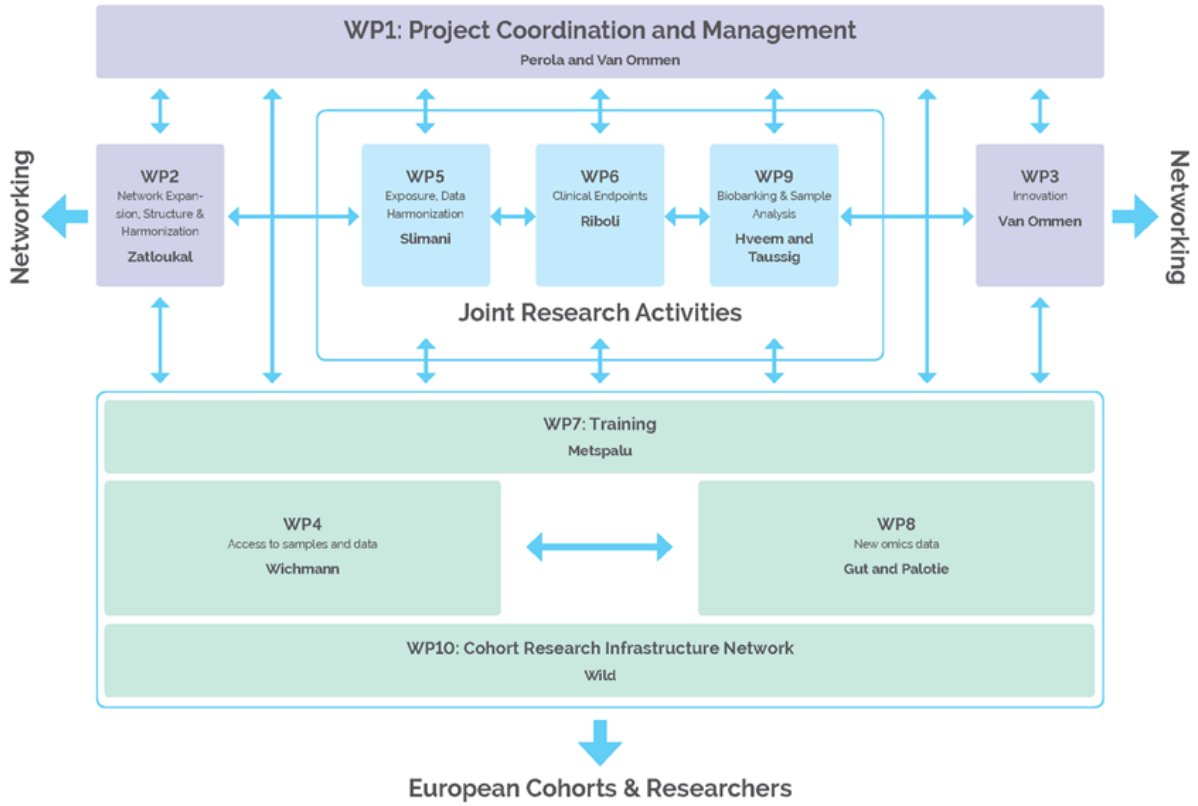
While streamlining access governance systems is not a straightforward task, there already are a number of initiatives on-going to rationalize and harmonize access policies and procedures across Europe. A promising platform for increased access harmonization, centralization and e-governance is represented by a pan-European research infrastructure BBMRI-ERIC (Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium). As a focused extension of BBMRI, BBMRI-LPC brought together 20 large prospective cohort studies from 10 countries and two EU-wide multinational cohort networks with a key objective to promote collaborative transnational research on prospective cohorts and analyse the gaps and needs involved.

BBMRI-LPC aimed to increase utilization of large sample collections for research on human health through networking, improving harmonization and providing solutions for improved transnational access. The project activities were organized through ten Work Packages (Table 1; Figure 1): WP4 and WP10 encompassed the actual access provision procedures; WP2 focused on the networking, ethical and legal activities; WP3 surveyed the landscape of European public-private interactions; WP5 and WP6 promoted harmonization of cohort data with emphasis on exposure variables and clinical endpoints; WP7 disseminated knowledge and training from established biobanks to emerging ones; WP8 conducted specific types of omics analyses for the selected access projects; and WP9 performed high-level research on the development of biobanking services and advanced techniques for protein analyses.

Table 1. List of the BBMRI-LPC work packages (WP) and the respective WP leaders.

WP no.	WP title	WP leader(s)
WP1	Project Coordination and Management	Markus Perola (Coordinator)
WP2	Network expansion, structuring and harmonization	Kurt Zatloukal
WP3	Innovation	Gert-Jan van Ommen (Co-Coordinator)
WP4	Cohort Research Infrastructure: Transnational Access	Erich Wichmann
WP5	Exposure data harmonization	Nadia Slimani
WP6	Clinical endpoints	Elio Riboli, Marc Gunter
WP7	Emerging biobanks in Eastern Europe: coordination, education, training and dissemination	Andres Metspalu
WP8	Access to upgraded data	Ivo Gut
WP9	Research on sample management and analysis	Kristian Hveem, Mike Taussig
WP10	Cohort Research Infrastructure Network	Paul Brennan, Mattias Johansson

Figure 1. The BBMRI-LPC work package structure.



1.2.2 Overall objectives

The overall objectives of the BBMRI-LPC project were as follows:

- To promote collaborative transnational research on prospective cohorts and analyze the gaps and needs involved by providing free transnational access for users selected by open pan-European scientific calls;
- To generate and provide access to whole-genome sequences, transcriptome, proteome, metabolome and methylome data within the framework of selected access studies thereby upgrading the value of stored samples;
- To evaluate and improve harmonization of individual data on health, lifestyle and other exposures;
- To develop and implement harmonized definitions of diseases;
- To improve biobanking and research technologies and develop innovative solutions facilitating high-quality, fair access to samples and data;
- To build a network transferring expertise of established European large-scale biobanks to new biobank initiatives under development in other countries;
- To facilitate new public-private partnerships involving large-scale prospective cohorts and strengthening existing ones, allowing transparent industrial access to academic expertise.

1.2.3 BBMRI-LPC Partners

BBMRI-LPC brought together 32 Partners, including 29 leading research organizations, two law companies and one biotechnology company across Europe and in Canada (Table 2). The project was led by Professor Markus Perola from University of Helsinki and co-led by Professor Gert-Jan van Ommen from Leiden University Medical Centre.

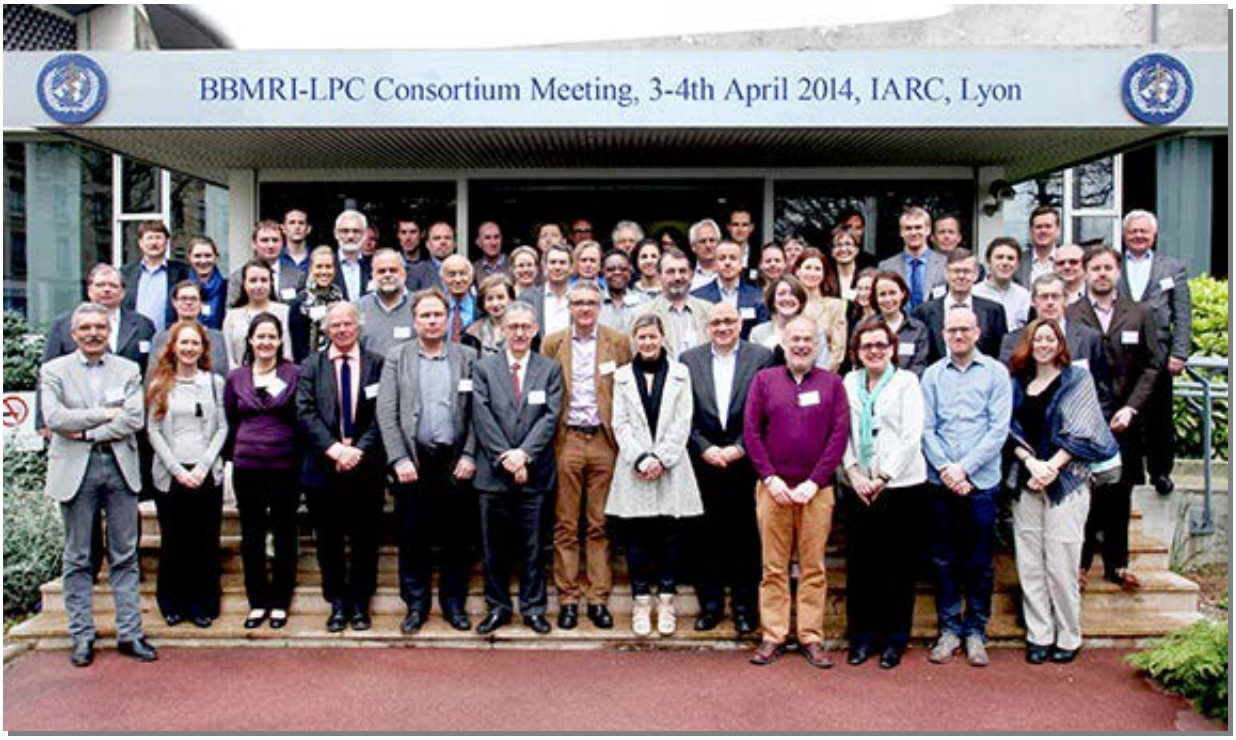


Table 2. List of BBMRI-LPC beneficiaries, respective countries and key personnel.

No	BBMRI-LPC Partner	Country	Key personnel
1	University of Helsinki	Finland	Markus Perola, Coordinator [WP1 leader] Eero Vuorio, Birgit Simell
2	Leiden University of Medical Centre	The Netherlands	Gert-Jan van Ommen, Co-coordinator [WP3 leader]
3	International Agency for Research on Cancer IARC	France	Nadia Slimani [WP5 leader] Paul Brennan and Mattias Johansson [WP10 leaders] Laurene Bouvard
4	Imperial College London	United Kingdom	Elio Riboli and Marc Gunter [WP6 leaders]
5	Medical University of Graz	Austria	Kurt Zatloukal [WP2 leader] Peter Abuja
6	Karolinska Institute	Sweden	Nancy Pedersen
7	Wellcome Trust sanger Institute	United Kingdom	Eleftheria Zeggini
8	University Medical Centre Groningen	The Netherlands	Ronald Stolk
9	Helmholtz Center Munich	Germany	Melanie Waldenberger
10	Norwegian University of Science and Technology	Norway	Kristian Hveem [WP9 co-leader]
11	University of Tartu	Estonia	Andres Metspalu [WP7 leader]
12	University of Uppsala	Sweden	Ulf Landegren, Erik Bongcam-Rudloff, Tomas Klingström, Mats Hansson
14	Cambridge Protein Arrays Ltd	United Kingdom	Mike Taussig [WP9 co-leader]
15	University of Pecs	Hungary	Bela Melegh
17	The Research Institute of the Mc Gill University Health Centre	Canada	Isabel Fortier
18	Legal Pathways Institute for Health and Bio Law	The Netherlands	Jasper Bovenberg
19	deCODE Genetics	Iceland	Unnur Thorsteindottir, Frosti Jonsson
20	The National Institute for Health and Welfare	Finland	Kari Kuulasmaa, Anu Jalanko
21	International Prevention Research Institute iPRI	France	Pierre Hainaut
22	Latvian Biomedical Research and Study Centre	Latvia	Janis Klovins
23	Split University School of Medicine	Croatia	Ozren Polasek
24	Wroclawskie Centrum Badan EIT+	Poland	Lukasz Kozera
25	Technical University Munich-Department of Medicine	Germany	Erich Wichmann [WP4 leader] Gabriele Anton, Klaus Kuhn
26	Institut national de la santé et de la recherche médicale	France	Emmanuelle Rial-Sebbag, Anne Cambon, Georges Dagher
27	Medlaw Consult	The Netherlands	Evert-Ben van Veen
28	Maastricht University	The Netherlands	Piet van den Brandt
29	Norwegian Institute of Public Health	Norway	Per Magnus, Camilla Stoltenberg
30	The State Serum Institute	Denmark	Mads Melbye
31	University of Bristol	United Kingdom	Paul Burton, Madeleine Murtagh, Joel Minion
32	Biobanking and BioMolecular resources Research Infrastructure - European Research Infrastructure Consortium BBMRI-ERIC	Austria	Jan-Eric Litton, Markus Pasterk, Outi Törnwall
33	University of Milano-Bicocca	Italy	Marialuisa Lavitrano
34	Centre nacional d'anàlisi genòmica - Centre for Genomic Regulation CNAG-CRG	Spain	Ivo Gut [WP8 leader], Monica Bayes

1.2.4 Cohort studies participating BBMRI-LPC

The BBMRI-LPC network involved 20 large prospective cohort studies from 10 countries and two EU-wide multinational cohort networks. Three scientific calls were organized to offer European investigators the opportunity to gain free of charge transnational access to the bio-specimens and data available in participating cohorts (Table 3).

Table 3. List of cohort studies participating BBMRI-LPC.

Cohort acronym	Cohort name	Country
CONOR	Cohort of Norway	Norway
CONSTANCES	Constances	France
DECODE	Decode	Iceland
DNBC	Danish National Birth Cohort	Denmark
EGP	Estonian Genome Project	Estonia
EPIC	European Prospective Investigation into Cancer and Nutrition (network)	EU-wide
EpiHealth	Epidemiology of Health	Sweden
FINRISK	National FINRISK Study	Finland
GAZEL	Gazel	France
GCAT	Genomes for Life. Cohort Study of the Genomes of Catalonia	Spain
HEALTH 2000	Health 2000	Finland
HUNT	Nord-Trøndelag Health Study	Norway
JANUS	Janus Serum Bank	Norway
KORA	Cooperative health research in the region of Augsburg	Germany
LifeGene	LifeGene	Sweden
Lifelines	Lifelines Cohort Study	The Netherlands
MoBA	Norwegian Mother and Child Cohort Study	Norway
MORGAM	MONICA Risk, Genetics, Archiving and Monograph (network)	EU-wide
NLCS	Netherlands Cohort Study	The Netherlands
Rotterdam study	Rotterdam Study	The Netherlands
TwinGene	TwinGene	Sweden
UK Biobank	United Kingdom Biobank	United Kingdom

1.3. Description of main S&T results/foregrounds

BBMRI-LPC has successfully achieved its primary aim of promoting collaborative transnational research on prospective cohorts and analyzing the gaps in need for solution. On the way, improved tools and procedures for promoting fair access to samples and data have been developed.

New omics data has been generated upgrading value of samples stored in the BBMRI-LPC participating biobanks. Use of the rare disease biobanks and identification of novel causative variants and genes for rare diseases has been promoted through whole-exome sequencing.

The legal and ethical experts within BBMRI-LPC have actively contributed to discussion on various ethical and legal aspects related to the use of biobanks and cohorts, as well as in close collaboration with BBMRI-ERIC to ensuring accessibility of counselling for various ethical, legal and social issues (ELSI).

A functional communication Forum for transferring expertise from established European large-scale biobanks to biobank initiatives in emerging biobanking countries has been created. Collaboration with these early-stage biobanks has further been facilitated through active dissemination of knowledge via project website and a number of organized training events.

New public-private collaborations involving large-scale prospective cohorts have been facilitated, existing collaborations strengthened and development of Expert Centres catalysed, allowing transparent industrial access to academic expertise.

As a result of joint research activities within BBMRI-LPC, a scientific evidence base for cost-efficient introduction of higher performance instrumentation, methodologies and protocols in sample handling, management and analysis has been laid and followed up by testing and evaluation of the systems. Novel immunoassays for detection of biomarkers and antibodies have been developed and applied to biobanked samples.

During project's period of operation, BBMRI-LPC Partners have actively engaged and performed the above project activities and made their outputs efficiently available to the scientific community through presentations in conferences and meetings, publications in leading scientific journals, organisation of meetings or training events, and visiting other institutions.

1.3.1 Identification of current gaps and needs in transnational access process to facilitate standardization of procedures for sample and data sharing

The primary objective of BBMRI-LPC was to promote collaborative, transnational research on large prospective cohorts across Europe by providing access to the samples and data in cohorts participating BBMRI-LPC. This objective has been successfully achieved: in total, over 15,800 biospecimens and data on over 714,000 study participants from 16 European cohorts were transferred to the principal investigators (PI) of 11 access projects. Basic details of each access research project are shown in Table 4. Careful monitoring of access provision process in each individual access project enabled identification of specific bottlenecks of sample and data sharing in a centralized and concrete way.

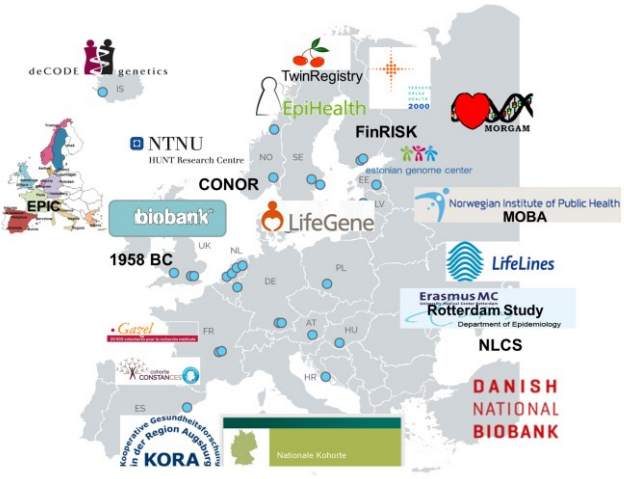


Table 4. The BBMRI-LPC access research projects and the numbers of samples delivered during the project lifetime.

No.	Title of the access project	Aim of the project	No of samples delivered
1	Markers of Imminent Myocardial Infarction (*MIMI*)	To identify novel biomarkers for risk of a first myocardial infarction within 6 months (imminent) of blood draw.	158 plasma
2	The metabolic pathways of renal cell carcinoma (*MetKid*)	To identify metabolic factors that mediate the association of obesity-related risk factors in kidney cancer aetiology.	1 508 plasma/serum 718 DNA
3	Discovery of early biomarkers for pancreas cancer (*PrePanCa*)	To identify early biomarkers for future occurrence of pancreatic cancer.	1 013 plasma/serum
4	Exposure to brominated disinfection by-products and prospective metabolic alteration	To address the association between exposure to disinfection by-products and the development of type II diabetes	1 037 urine/whole blood
5	Biomarkers of human papillomavirus (HPV) infection and risk of two increasing cancers	To evaluate the potential of using HPV-serology in early detection of HPV-related cancers.	2 654 plasma/serum
6	Metabolic Profiling and Colorectal Cancer Risk	To advance understanding of the mechanisms of colorectal cancer development by detailed assessment of biochemical pathways and novel metabolic intermediates.	2 606 plasma
7	Exploring the genetics of irritable bowel syndrome (*Bellygenes*)	To identify genetic factors contributing to the risk of irritable bowel syndrome (IBS).	*data only*
8	Biomarkers of ischemic stroke in prospective cohorts (*BiStroke*)	To quantify the risk spectrum of stroke by identifying a set of biomarkers based on incident data from large population-based cohorts..	1 466 plasma/serum 876 DNA
9	Identification of biomarkers for gallbladder cancer risk prediction – Towards personalized prevention of an orphan disease	To identify circulating biomarkers associated with gallbladder cancer risk.	736 plasma/serum
10	The influence of macronutrient dietary patterns on pregnancy	To explore association between macronutrient intakes consumed in pregnancy with the subsequent birth outcomes.	data only
11	Unravelling the role of bile pigments in colorectal cancer development and survival	To determine association of elevated circulating bilirubin levels with risk of colorectal cancer development and survival.	2 796 plasma/serum

Access to several cohorts simultaneously in a multinational research project proved to be challenging due to the heterogeneity of current access governance structures and guidelines. Regrettably, burden of this fragmentation seems to fall on the scientists. The following main bottlenecks were identified in access process and confirmed by feedback received from the access project PIs:

- ***Establishing Material Transfer Agreements.*** A vast majority of access project PIs reported a lengthy process in establishing the necessary Material Transfer Agreements (MTAs), which usually required several back and forth communications between each institute providing biomaterial, the institute using the biomaterial, and possibly also the center receiving the actual samples and performing analyses.
- ***Heterogeneous access processes.*** The access process to each cohort had to be conducted separately and differed from cohort to cohort. Thus, access project PIs were unable to learn from access gained to one cohort as access to another cohort would work differently.
- ***Uneven response times.*** Response time from the cohorts was as uneven, ranging from extremely responsive cohorts to slow ones with several reminders necessary.
- ***Actual availability of biomaterial.*** Even though catalogues displaying the type and number of cases occurring in a specific cohort study were in place, other researchers with previous studies had in some cases used up the collected samples.

  On the other hand, all of the granted access projects were practically case-control studies, mostly requesting for a small number of samples for specific research questions. Although these projects were scientifically

important and well-designed (and sometimes only possible in a multi-cohort design like in BBMRI-LPC), a number of cohorts were reluctant to break up their full series of samples for the use of such small sample numbers, as this would result in a set of cohort with samples missing from some individuals and thereby hamper the use of samples for research where the full cohort is needed. The cohorts would have probably consented for use, if there had been sufficient resources to analyse the full cohort instead of a case-control set only.

- ***Heterogeneous data transfer processes.*** Again, the access process had to be conducted for all cohort studies separately: data transfer had to be agreed upon with each cohort individually and procedures differed from cohort to cohort.

To summarize, standardized access processes (such as a common application template that could be submitted to several cohorts at the same time) and a centralized data access approach (or alternatively a flow chart showing at a glance the different steps required by each cohort) was urged by most access project PIs, together with a standardized MTA template. On a more technical note, harmonizing the way in which biomaterial is shipped was also requested (e.g. some samples are shipped in straws, while others are aliquoted into tubes). Availability of a dedicated contact person with in-depth knowledge of scientific aspects and procedures specific to the cohort would greatly assist the access project PIs by guiding them through the application process.

At the time when BBMRI-LPC ends, several of the access projects are still in their early stage of investigation: analyses are progressing, but interpretation of the results will require a few more months before being published. Nevertheless, BBMRI-LPC has played a central role in mediating production of important downstream scientific findings by enabling the access project PIs to conduct their research on multiple large prospective cohorts.

1.3.2 Development of improved procedures and tools for promoting fair access to high-quality samples and data

1.3.2.1 Extension of the catalogue of European biobanks

To provide a structured overview of participating cohorts and support to external investigators in gaining access to the resources available through BBMRI-LPC, the BBMRI-EU Cohort Catalogue was extended to adapt to the specific needs of large prospective cohorts. The result is *BBMRI-LPC Cohort Catalogue,* a database application publicly accessible at http://www.bbmri-lpc-biobanks.eu/catalogue.html. The details provided in the BBMRI-LPC catalogue include, among others, the cohort contact information, cohort background, focus, objectives, diseases of interest and financing. Moreover, the number of samples available in each cohort are described by type of the sample material, and a comprehensive search function is provided. At the end of BBMRI-LPC, it has been agreed that the BBMRI-LPC cohort catalogue will be taken over and sustained by BBMRI-ERIC.

1.3.2.2 Financial principles regarding access provision

Main financial principles and rules for compensation of access to samples and associated data within the BBMRI-LPC network needed to be outlined at the early stage of project. To determine costs related to sample provision in the participating cohorts, estimated sample unit cost calculations from each cohort were requested. Based on received information, the estimated sample unit cost originally planned for BBMRI-LPC had to be increased. Nevertheless, even the elevated estimated unit cost still caused problems for some cohorts using fixed price lists with considerably higher access costs compared to the estimated unit cost. In most cases, however, these cohorts agreed to accept the lower compensation in light of the overall benefit to them of participation in BBMRI-LPC. Another challenge for some cohorts was the refunding scheme on sample basis. As work-load at cohorts for projects asking for small numbers of samples is usually as high as (or even higher) than in projects asking for a whole series of samples, the compensation obtainable for participation in the BBMRI-LPC access projects could not fully cover the incurred expenses for all of the cohorts.

Within the course of project, a web-based cost calculation tool was developed to standardize and facilitate access cost calculation in population-based cohorts within BBMRI-LPC and beyond. The *BBMRI-LPC cost calculator* is publicly accessible on-line at https://epi.helmholtz-muenchen.de/tools/calc/. At the end of BBMRI-LPC, it has

been agreed that the cost calculator will be taken over and sustained by BBMRI-ERIC. Further expansions to the cost calculator are being planned, including a publicly accessible database on costs and user fees in European biobanks.

1.3.2.3. Harmonization of exposure data in participating cohorts

Research infrastructure to support large European cohort networks with data harmonization, data handling, data access and data processing is currently not readily available. A major task in BBMRI-LPC was to perform a thorough inventory of the resources available within participating cohorts and to propose improvements for the harmonization of individual-level participant data on lifestyle, environmental and other available exposures. The aim was to provide users with standardized information about participating cohorts with sufficient details to evaluate suitability for their research needs. A tool used for the exposure data inventory was *Maelstrom research platform*, an application which is specifically adapted to catalogue large prospective cohorts. It allows users to have direct access to complete exposure variable data dictionaries of each cohort, as well as provides a tool for graphical illustration of data collection points, data harmonization and downstream statistical analysis.

The harmonized resources have been made available through the launch of a *BBMRI-LPC Exposure Data Library* accessible on the BBMRI-LPC Access Website (http://bbmri-lpc.iarc.fr/). In addition to compiling the exposure data inventory, a standard operating procedure (SOP) was developed to support harmonization of individual exposure data used in the access projects. One of the access projects (*PrePanCa*; see Table 4) was used as a pilot study with a selected set of variables for evaluation of the overall harmonization process in a real case study scenario together with soft and hard support infrastructures. This enabled identification of main gaps in exposure data harmonization and provision of recommendations for future improvements.

1.3.2.4 Harmonization and refinement of clinical endpoint data in participating cohorts

Using an improved clinical endpoint definition that takes note of revised disease subgroups (such as those classified using improved molecular or histopathological data) is suggested to open novel insights into risk factors for disease. Heterogeneity of clinical endpoint definitions, as used by the participating cohorts, was evaluated to assess whether they could be refined using updated data on molecular and pathological characteristics. In addition, support was offered to the access project PIs for harmonization of clinical endpoint data across multiple cohorts. Utilizing the information gathered from participating cohorts together with the newly harmonized data from the *BBMRI-LPC Exposure Data Library* (see above), several analyses using the redefined clinical endpoints in a number of access projects have been conducted. One goal was to compare the results obtained with the revised definitions to those using the traditional clinical endpoint definitions. Such analyses are on-going with specific focus on diabetes, insulin resistance and cancer, and several publications in peer-reviewed scientific journals are anticipated to result from these efforts.

1.3.3 Upgrading value of samples stored in biobanks through omics analyses

1.3.3.1 Whole-genome genotyping and metabolomics for the access research projects on common chronic diseases

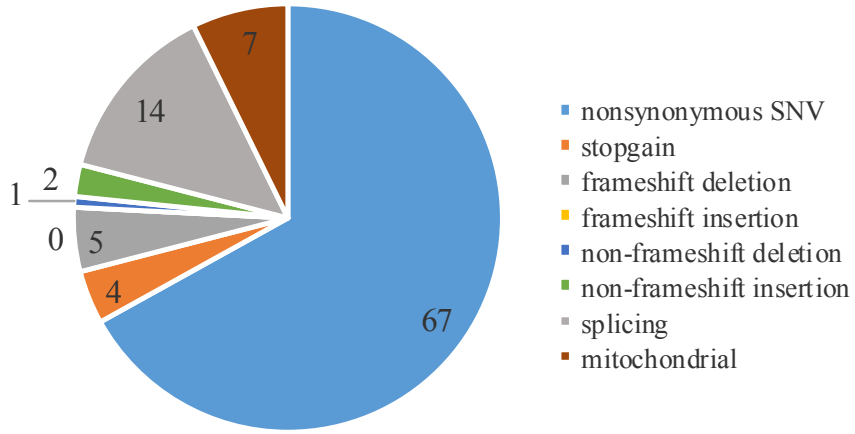
Rapid development of high-throughput techniques has enabled broadening of the selection of phenotype and genotype data linked to the individual samples deposited in prospective cohorts and biobanks. Such data includes traditional phenotype, imaging and clinical chemistry data, and now to an increasing extent also genome-wide sequencing, genotyping, transcriptomic and metabolomic data. In the BBMRI-LPC scientific calls 1-3, metabolomics and whole-genome genotyping analyses were offered free-of-charge for the access projects that were demonstrated to benefit significantly from these analyses. As a result, research on new biomarkers and metabolic factors associated with diseases has generated new genome-wide genotyping data in four access projects and targeted or untargeted metabolomic data in five access projects, thereby adding value to samples stored in the participating biobanks.

1.3.3.2. Whole-exome sequencing of rare diseases

The BBMRI-LPC whole-exome sequencing (WES) call offered an opportunity to genetically diagnose rare disease patients with samples deposited in biobanks from the *EuroBioBank*, a network of 23 rare disease (RD) biobanks holding close to 150 000 biological samples (http://www.eurobiobank.org/). Specific objectives of this initiative were to promote use of biobanks for rare diseases, to promote utilization of cutting-edge next-generation sequencing technology for the identification of novel causative variants and genes, to diagnose rare disease patients at a molecular level, and to promote data sharing for rare disease research to enable future discoveries.

Seventeen projects were awarded with the range of targeted diseases including neurosensorial, neuromuscular, neurological, cardiovascular, developmental, oncological and metabolic disorders. Whole exome sequencing at more than 85x coverage was performed for a total of 813 samples, including at least 237 unrelated undiagnosed patients. Robust bioinformatics pipelines were used to identify and annotate all the variants. The resulting genomic data and the available phenotypic data were uploaded into the *RD-Connect analysis platform* (https://platform.rd-connect.eu/). So far, strong candidate variants have been identified in 135 unrelated cases (i.e. 57% of the analysed patients): 84 pathogenic or likely pathogenic and 51 that require additional studies (Figure 2). The results from the WES call projects will be published as a collaborative effort between the applicant's group and the supporting investigators. The BBMRI-LPC support and collaboration will be acknowledged in all forthcoming communication and publications. Overall, the BBMRI-LPC WES call process was very smooth and efficient. Most samples and data were already deposited in the *EuroBioBank* and dissemination for the call was very active and had a good coverage in the rare disease community, already collaborating closely and knowing each other well.

Figure 2. Summary statistics (%) of the strong candidate variants identified.



1.3.4 Active contribution to the ethical and legal aspects in the field of biobanking

1.3.4.1. Specific ethical and legal services within the BBMRI-LPC project

The legal and ethical experts within BBMRI-LPC have collaborated actively to provide advice on various legal and ethical matters related to the cross-border research co-operations. Close collaboration with the BBMRI-ERIC Common Service ELSI was initiated at an early stage of BBMRI-LPC and continued with several joint collaborations.

To facilitate sample and data sharing, a standardized BBMRI-LPC template for a Data/Material Transfer Agreement was developed and finalized in 2015 in collaboration with legal experts of the BBMRI-LPC network and P3G (http://p3g.org/). In order to develop a framework to facilitate accurate acknowledgement of bio-resource use (particularly the cohorts), in publications and other dissemination activities, a *Bio-resource Research Impact Factor (BRIF)* initiative was integrated into the BBMRI-LPC work plan. Closer to end of the project, specific issues identified during the course of BBMRI-LPC were followed up and an effort made to design solutions for promoting fair and responsible data-sharing while improving public private partnership.

1.3.4.2 General ethical concerns for the future developments of biobanks and property issues

The legal and ethical experts within BBMRI-LPC have actively contributed to general discussion about ethical concerns for the future developments of biobanks by giving presentations in a number of international congresses and meetings.

A comprehensive report has been compiled describing the ethical and legal basis for permitting transnational sharing of data and samples in Europe, with a particular focus on the implications of the recently adopted General Data Protection Regulation (GDPR), and is provided in the project deliverables.

During the BBMRI-LPC project period, several issues related to generation and use of massive amounts of data, 'Big Data', have arisen and will be the next questions for future use of data and samples stored in the biobanks. To address them, the consequences of producing Big Data have been studied more deeply and some innovative solutions for supporting fair data-sharing embedded in ethical and legal compliance have been proposed in the project deliverables. In addition, the challenges of intellectual and biological property have been addressed as a contribution to identifying current roadblocks for data sharing.

1.3.5 Harmonization, structuring and expansion of the biobanking network

1.3.5.1 Promoting synergies and interoperability with BBMRI-ERIC

In addition to the main objective of promoting transnational access, synergies between BBMRI-LPC and BBMRI-ERIC were also promoted in three other main areas:

- ***Ethical and legal compliance.*** A close collaboration with the BBMRI-ERIC Common Service ELSI was established. As a result of this collaboration, BBMRI-LPC has contributed to development of the Human Sample Exchange Regulation Navigator (hSERN) and the WIKI legal, tools for providing users with information on theoretical and practical legal aspects for exchanging human biological samples across borders. Another concrete result of collaboration has been the first meeting of BBMRI Research Ethics Committees (RECs) entitled '*Towards mutual REC-ognition*' organized in conjunction with the Europe Biobank Week 2016 (Vienna, Austria).
- ***Quality management.*** In biobanks containing samples from large population cohorts, quality is of crucial importance. To obtain an overview of the baseline sample quality, a sample quality proficiency testing of nine BBMRI-LPC participating biobanks/cohorts was performed as part of the BBMRI-LPC Quality Management (QM) scheme. Serum and plasma samples from large population cohorts collected at different biobanks under different standard operating procedures (SOPs) were evaluated for quality and suitability for metabolomic

analyses. The results showed that sample quality in general was high even after prolonged storage, and that the samples were well suited for the metabolomic analyses, though they could still be distinguished according to the biobank from which they were obtained. The work has been continued by evaluating suitability of samples from multiple sources for joint analyses.

- ***Harmonisation of biobanking technologies.*** A software tool has been developed for harmonization of individual SOPs with the CEN/TC Technical Specifications for pre-analytical processing of biological samples. The *SOP mapping tool,* implemented jointly by BBMRI.at, BBMRI-ERIC, RD Connect and BBMRI-LPC, facilitates the implementation of SOPs according to European quality standards and also permits checking the existing SOPs for compliance with the quality standards.

1.3.5.2 Promoting synergies with other ESFRI Biological and Medical Sciences infrastructures

A coordination board for the current European Strategy Forum for Research Infrastructures (ESFRI) in Biological and Medical Sciences (BMS) was chaired for several years by the BBMRI-LPC representative, Professor Eero Vuorio. Several board meetings were held, in which BBMRI-LPC provided support for the other infrastructures in regard to expertise in biobanking and in requirements for accessing human biological samples. Subsequently, to reach the highest degree of strategic collaboration and synergies, twelve BMS research infrastructures (RI) signed a Memorandum of Understanding to establish the BMS RI Strategy Board.

1.3.5.3 Global integration with international biobanking organisations

In close collaboration with BBMRI-ERIC, BBMRI-LPC has actively participated in integration activities with other European and global biobanking organizations (e.g. P3G, BioMedBridges, B3Africa). In the seminar entitled '*Biobanking: A Gateway for Health'* organized by BBMRI-ERIC on November 18, 2014 in Brussels, the topic of global integration of biobanks was, among others, presented to the European institutions, industry and the research and stakeholder community. As well as presenting BBMRI-ERIC and its role in European research, industrial development and healthcare, the integration of European biobanking into an international context was highlighted with examples detailing co-operation with China and Africa, and by emphasizing the need for global standardization of biobanking.

1.3.5.4 Creating a Forum for transferring expertise from established biobanks to new emerging biobanks

Collaboration and networking at an early stage is a vital aspect in promoting use of large prospective cohorts. In order to facilitate development of early-stage initiatives in the emerging biobanking countries, the existing established biobanks within the BBMRI-LPC network have actively offered their support and expertise to the new, arising biobanks. A communication platform for transferring expertise from established European large-scale biobanks to new initiatives in the emerging biobanking countries was created by organization of four annual Biobank Forum meetings in Graz, Austria (2013); Tallinn, Estonia (2014); Budapest, Hungary (2015); and Vienna, Austria (2016). Three of the Forum meetings were organized in conjunction with other biobanking-related events.

Several important achievements and observations have been made through organizing the Biobank Forum:

- ***Forum achieved its aimed structuring effect on the European biobanking community***. By recruiting participants from most Eastern European countries, BBMRI-LPC Forum has contributed to a gradual build-up of the European biobanking community (Figure 3). In the course of annual Forum meetings, participation of the emerging biobank countries gradually increased (Table 4) creating more informal discussions and information exchange between the emerging and established biobanks.
- ***A comprehensive network of national biobanking contact persons was established.*** A total of 21 emerging biobank countries from Eastern Europe and beyond have been represented in at least one Forum meeting (Figure 3; Table 4). As most of the BBMRI-ERIC Member and Observer States have also been represented in the Forum meetings, overall coverage of the established European biobanking community can be considered nearly complete. Through organization of practical training courses targeted primarily at younger researchers, contacts have also been identified in Balkan countries, for which no representatives have been present at the Forum meetings.
- ***Need for continued EU support for clinical biobanking was identified***. In most of the emerging biobank countries, biobanks have been initiated in a clinical setting, often based on material stored in pathology

departments. Typically, biobanked material and related data has been (or are being) collected from specific disease groups. Although practical aspects of clinically oriented biobanks are very similar to those in large population cohorts, there is an obvious need to support also networking platforms for clinically-oriented biobanks in Europe.

- ***Need for national and political support for population-based biobanks was identified***. In the course of BBMRI-LPC, participants from emerging biobanking countries showed clear interest in the population cohorts and biobanks. Nevertheless, we are aware of only a few new national population-based cohort initiatives, for example in Latvia and Croatia. It is clear that a considerable amount of time and political support is needed to establish new national cohorts/biobanks.
- ***Continuation of the Forum in context of the BBMRI-ERIC activities.*** The four BBMRI-LPC Forum meetings were judged to be successful in creating an information exchange platform between emerging and established biobanks, both by the participants and organizers. Consequently, it was decided already in 2015 that after the end of BBMRI-LPC an annual biobank Forum meeting will be continued by BBMRI-ERIC.

Table 3. Participation of the emerging biobank countries and non-BBMRI-ERIC Member countries in the Biobank Forum meetings in 2013-2016

Emerging biobank countries and non-BBMRI-ERIC Member countries participated at least one Forum meeting 2013-2016		
#	Country	Year
1	Bulgaria	2013, 2014, 2015, 2016
2	Croatia	2013, 2014, 2016
3	Cyprus*	2013, 2014, 2015, 2016
4	Czech Republic*	2016
5	Denmark and Faroe Islands	2015. 2016
6	Georgia	2015. 2016
7	Hungary	2013, 2014, 2015, 2016
8	Indonesia	2016
9	Ireland	2013, 2016
10	Israel	2013
11	Kazakhstan	2014
12	Kosovo	2016
13	Kuwait	2014
14	Latvia*	2013, 2014, 2015, 2016
15	Lithuania	2013, 2014, 2016
16	Luxembourg	2014, 2016
17	Poland*	2013, 2014, 2015, 2016
18	Portugal	2013, 2015 ,2016
19	Romania	2014, 2016
20	Russia	2015, 2016
21	Slovenia	2015, 2016
22	Slovakia	2015
23	South Africa	2016
24	Spain	2014, 2016
25	Turkey*	2013, 2014
26	Ukraine	2013, 2015, 2016
27	Uzbekistan	2016
28	Vietnam	2014

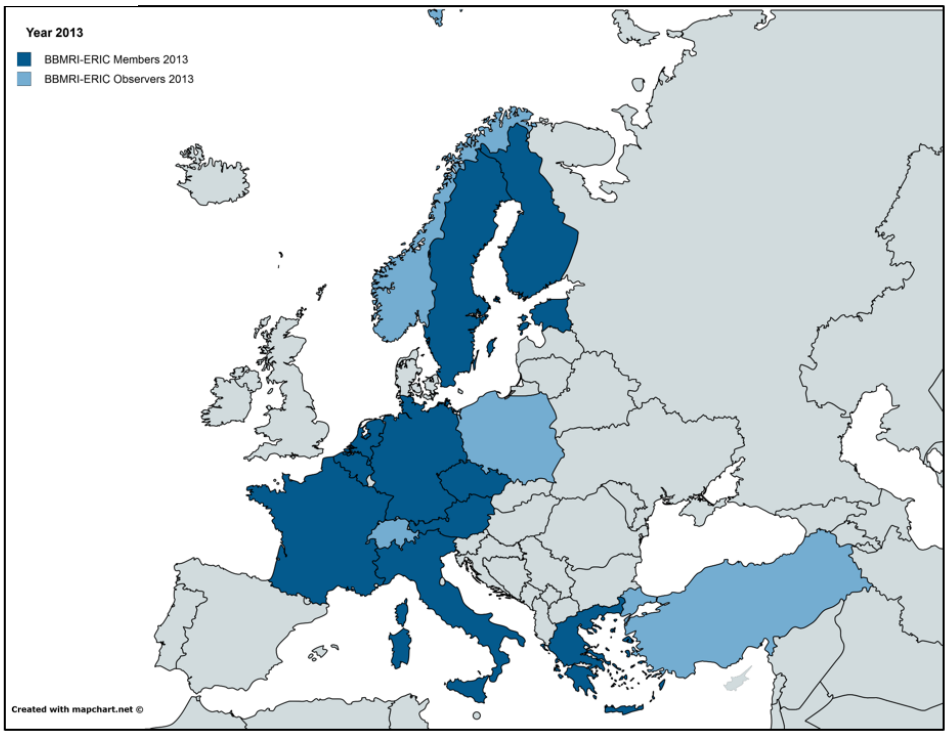
Non-BBMRI-ERIC Member countries shown interest to Forum without participation 2013-2016		
#	Country	Year
1	Belarus	2016
2	Bosnia-Herzegovina	2014, 2015
3	Ghana	2015
4	Serbia	2013, 2016

Non-BBMRI-ERIC Member countries invited to Forum without response 2013-2016		
#	Country	Year
1	Albania	no response
2	Iceland	no response
3	Montenegro	no response
4	Macedonia	no response

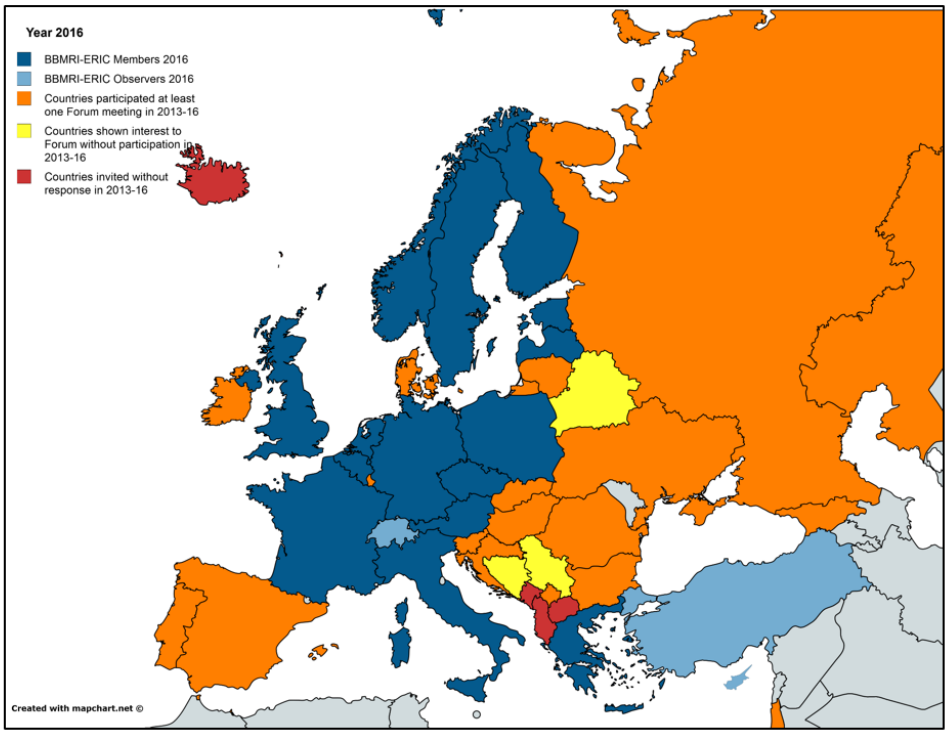
*Status of the country changed to BBMRI-ERIC Observer or Member within 2013-2016

Figure 3. Growth of the European biobanking community during the BBMRI-LPC project in 2013-2016.
Panel A, BBMRI-ERIC Member and Observer countries when BBMRI-LPC was initiated in 2013.
Panel B, BBMRI-ERIC Member and Observer countries in November 2016 together with countries that have been represented in at least one BBMRI-LPC Forum. Also shown are countries where contacts have been identified, although they were unable to attend any of the Forum meetings in 2013-2016.

Panel A



Panel B



1.3.6 Training and education directed towards the emerging biobanks

1.3.6.1 Identification and database of the early-stage population biobanks

A database of the early-stage population biobanks in Europe has been created with an assessment of their developmental stage. More than 100 emerging biobanks or sample collections from the Eastern-Europe region are included in the database, which also contains collections from non-EU countries (e.g. Georgia, Ukraine, Russia, Kazakhstan) and countries outside Europe (e.g. Kuwait, Vietnam).

1.3.6.2 Training and education targeted at the early-stage biobanks

A link to a network and expertise of the existing large-scale biobanks was provided for scientists and other personnel of the emerging biobanks, particularly from Eastern Europe, by organisation of workshops and courses on practical biobanking, as well as by on-site visits to the Estonian Biobank. Several training courses, workshops and exhibitions on biobanking were also organized locally by BBMRI-LPC-participating institutes.

1.3.6.3 Active dissemination of knowledge and expertise to the early-stage biobanks

The BBMRI-LPC website was used for active dissemination of biobanking-related information. A *BBMRI-LPC Biobanking Helpdesk* aiming to assist the emerging European biobanks in various biobanking-related issues was established in the first quarter of BBMRI-LPC. Questions could be sent through an on-line web form available on the BBMRI-LPC website. Presentations of previous BBMRI-LPC training events have been uploaded on the project website under the topic *Biobanking ABC*. A *Handbook of Practical Biobanking* containing various biobanking-related strategies, guidelines, publications, presentations and white papers has been compiled and made accessible in electronic format on the internal area of project website (due to potential copyright issues no open access could be provided).

1.3.7 Monitoring existing public-private collaborations and facilitating new partnerships between industry and academia for transparent sharing of expertise in these fields

Building new public-private partnerships between large-scale prospective cohorts and industry was supported in the course of BBMRI-LPC, along with strengthening existing ones. Development of BBMRI Expert Centres each supported at its own national level was catalysed and close interactions between them and European industry were brought about through a combination of meetings, publications, web information as well as personal contacts.

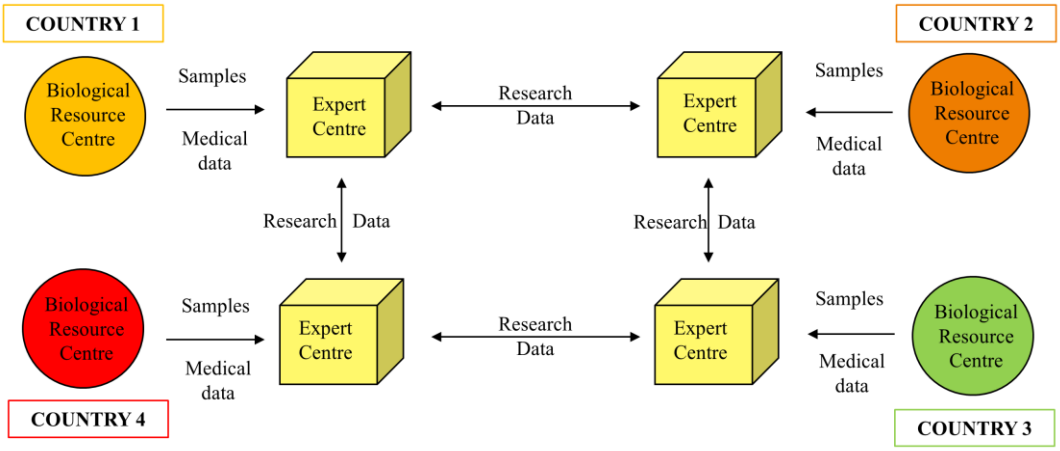
The first examples of public-private partnerships were established already in the early phase of BBMRI-LPC, despite the fact that international crisis had hit the pharma companies hard and made them less open to public-private collaborations other than ‘classical' 1:1 interactions. In a pilot use case of BBMRI-NL, an attractive and fair public-private benefit-sharing model was established with Pfizer and Complete Genomics. A white paper (van

Ommen *et al.* 2015*)* was developed between many BBMRI-LPC parties presenting the *BBMRI-ERIC Expert Centre* concept (Figure 4)*,* a new model for academic-industry collaboration, with several examples of on-going public-private collaborations (e.g. *EXCEMET*, *SciLifeLab* and *Lifandis AS*).

Subsequently, two BBMRI-ERIC Expert Centers, *CBmed* (Austria) and *ATMA-EC* (Italy)*,* were officially established in 2016-2017. Both centers perform not-for-profit public-private research for identification and validation of biomarkers and conduct translational research under strict and transparent quality conditions, helping to bring products to clinical practice. In parallel, several BBMRI-LPC parties have initiated regional, often bilateral public-private interactions. Both the BBMRI-LPC quality management (QM) scheme and the access research projects have yielded new academic-industry interactions. New genomic, proteomic, and metabolomic tools and methods have been developed and applied in the above public-private collaborations. First results of multi-parametric analysis have been obtained yielding early systems-level understanding in health and disease.

In the final phase of BBMRI-LPC, with the economies on the rebound, a series of 19 interviews was held with key opinion leaders to assess views on Expert Centres and public-private partnerships. The interviews showed that European biobanks are currently widely engaged in public-private collaborations and consider establishing Expert Centres or joining existing ones (Hämäläinen *et al.*, manuscript under review). These Expert Centres already collaborate with pharmaceutical and biotech industries, as do two emerging, very large public-private consortia *Genomic Research Consortium GRC* and *FinnGen*, engaging several biobanks and academic parties and involving a substantial number of international pharmaceutical companies. Many public parties in both consortia are BBMRI-LPC Partners.

Figure 4. The BBMRI Expert Centre model.



1.3.8 Scientific evidence-base for optimized sample handling and management

The increasing level of interoperability between the BBMRI-LPC-participating biobank centres was utilized to create an evidence-based large-scale development and evaluation platform for biobank services, and new processes and protocols. A network encompassing several large-scale biobanking facilities was established and a viable and enthusiastic core group of up to 40 experts engaged with focus on quality of lab ware, storage temperatures and other critical factors for preserving sample integrity. Services provided at the collaborating centers were mapped in terms of processes, instrumentation, quality control measures and results, cost and speed. The accumulated data has been assembled on a large number of biobank procedures, providing the basis

for cost-efficient introduction of higher performance instrumentation, methodologies and protocols in sample handling and management, as well as improved DNA and RNA-extraction protocols.

A recommended standardization scheme for sample handling, *BRISQ* (*Biospecimen Reporting for Improved Study Quality*), has been established and provided as a dynamic web-based document, where information can be added or revised, as required. To facilitate availability and sharing as well as to improve scientific quality, the laboratory protocols for studies on biobank procedures have been entered into the Molecular Methods Database *(MolMeth;* www.molmeth.org). To ensure a more sustainable solution, it has been agreed with BBMRI-ERIC Common Service IT to organize a dynamic database, *Common Catalogue for Biobank Services (CCBS),* listing services as web-based business cards, a model developed initially by the Biobanking Analysis Resource Catalogue *(BARC)*, a publicly accessible web resource of analytical technology services and products used in biomedical research, listing expertise and molecular resource capabilities available at research centres and biotechnology companies (http://www.barcdb.org/).

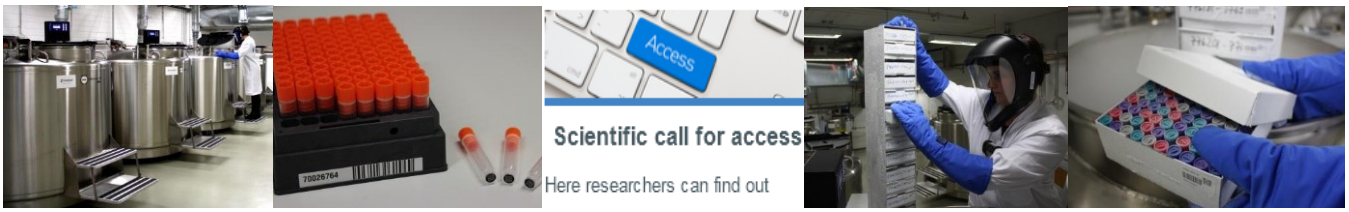
1.3.9 Development of advanced techniques for protein analysis based on antibody-DNA conjugates and protein microarrays

Novel immunoassays with high sensitivity and specificity for detection of biomarkers and antibodies to be used for research on disease mechanisms and diagnostics have been developed within BBMRI-LPC. These techniques were designed to measure many proteins in parallel, both in solution and on microarrays, and to be applied to biobanked series of plasma/serum samples, including consecutive samples. The major tools used were large-scale arrays of human proteins *(HuProt™ arrays)*, with over 20 000 proteins arrayed on a single microscope slide, and proximity ligation assays in which pairs of antibodies with conjugated oligonucleotides give rise to DNA ligation or DNA polymerisation products upon proximal binding to target proteins. Such assays are ideally suited for detection of autoantibodies and protein biomarkers, respectively. A series of variant techniques has been developed, in which proteins are first captured on a solid support before interrogation with proximity probes (*PLARCA*), offering increased sensitivity of detection. This assay can be implemented with standard equipment available in most clinical diagnostic and research labs (Ebai *et al*. 2017).

Strategies to construct very low-cost biobanks with consecutive samples from large numbers of individuals for protein analysis were investigated by drying drops of blood on paper for analysis by *Proximity Extension Assay (PEA)*. The samples can be collected by the donors themselves by pricking their fingers and sending the paper sample by mail, enabling both extensive biobanking and wellness profiling. A set of 92 protein markers have been demonstrated to preserve their detectability very well upon drying and a majority of proteins were stable over several decades of storage (Bjorkesten *et al*. 2017). In a related study, conditions for the collection of plasma samples were identified to avoid distorted protein levels due to release from blood cells (Shen *et al*. 2017).

In a disease analysis application, the performance of the HuProt™ protein arrays in detection of antibodies in sera of patients with primary Sjogren's Syndrome (pSS) was evaluated to determine if any novel targets of autoantibodies could be identified which might have diagnostic use or reveal mechanisms of the disease. Using sera from 20 patients and 20 matched controls, the HuProt™ arrays correctly detected all predicted pSS antibodies and several for coincident autoimmune conditions. A number of autoantibodies against new potential target antigens were also identified, providing novel targets for characterisation and evaluation.

In another study, plasma autoantibodies in samples from 50 elderly subjects from the Estonian Biobank cohort were profiled on HuProt™ protein arrays to determine any predictive association between the occurrence of autoantibodies with short-term risk of death within a 5-year period. The subjects included both living individuals and individuals who had died within 5 years of joining the biobank. 121 antibodies which differed significantly between the two groups (died or alive after 5 years) were identified and of these, a set of 11 antibodies was found which could predict mortality with high sensitivity and specificity. In order to validate the conclusions of this study, and to assess their value for development into predictive and preventive clinical biomarkers, analysis of a larger cohort will be required and will be completed after the conclusion of BBMRI-LPC. The study provides a novel and intriguing means of assessing the risk of mortality in the aged population.



1.4. Potential impact, main dissemination activities and exploitation of results

1.4.1 Potential Impact

Coordination of large collaborative studies involving transnational access to population cohorts in Europe is increasingly complex and time consuming. While BBMRI-LPC has had its undeniable main impact in charting the possibilities and pitfalls of transnational sample and data sharing between individual researchers and large cohorts, project has demonstrated the scientific potential of fostering collaboration across large prospective cohort studies with extensive exposure, clinical endpoint data and biological samples. In the area of both common and rare disease, it has been the first of its kind to offer external applicants funded access to cohort samples and data. BBMRI-LPC has shown the complexity of coordinating large population-based studies with multiple layers of complex infrastructure, and brought into light the current gaps and needs for data sharing, data harmonization, and research infrastructure support and sustainability. This information is envisaged to promote epidemiological, clinical and therapeutic research, thereby benefitting entire biobanking and biomedical communities.

Eleven scientifically outstanding research projects were granted access within BBMRI-LPC. Samples for the access projects have been successfully delivered and excellent scientific results are expected or in some cases already achieved. The BBMRI-LPC access projects have provided a proof of principle showing that it is possible to facilitate transnational access projects centrally in a coordinated and homogeneous fashion, with important gains in efficiency. They have also made visible specific bottlenecks, through solution of which prospective cohorts can improve the way they operate for better efficacy. A simple and concrete example was the importance of having (at least) one individual as a primary contact point with intimate knowledge of the specific idiosyncrasies of the individual cohort to guide external investigators through the access process. Experience in BBMRI-LPC clearly show that basic resources for administrative duties are essential at the cohorts. Integration and use of the main BBMRI-LPC outcomes should provide users, scientists, policy makers and funders with new insights into the potentials and needs for future research infrastructures and investments in Europe as well as roadmaps for coming work plans and priorities. Cohort studies within Europe and beyond are envisaged to benefit from such advice in their day-to-day operations.

The insights obtained into transnational access, both the previously known and newly identified hurdles, have been documented together with proposed solutions for improvement in a manuscript submitted for publication (Simell *et al*). The experience gained in the course of BBMRI-LPC will be used optimally to help BBMRI-ERIC in its aim of facilitating access and encouraging collaborative transnational research projects. To this end, several concepts and solutions developed during BBMRI-LPC are planned to be sustainably integrated within the BBMRI-ERIC Work Plan.

The BBMRI-LPC project has provided important insights for optimising standardization and retrospective harmonization of exposure and endpoint data, while preventing duplication of work and fragmentation of resources. In addition, BBMRI-LPC enabled identification of current gaps and needs in data access and sharing, retrospective data harmonization, as well as support and cost-effective sustainability of research infrastructure. Experience gained in the course of the project has shown that there is a strong demand for up-to-date information on the available resources, clinical data and clinical endpoints. Direct contact of the cohort representatives with the access project PIs was shown to be of utmost importance in order to identify the project's requirements and to harmonize the data with respect to the availability of data and samples in each cohort. This step can only partly be covered by various on-line tools, such as catalogues, and needs to be

supplemented by administrative staff at each cohort that have a good knowledge of the cohort's resources and set-up and can navigate the external investigators through the process to the correct samples and data.

The BBMRI-LPC call for whole-exome sequencing (WES) of rare diseases significantly reinforced the collaboration between the European rare disease biobanks as well as investigators of rare diseases. It has promoted use of the rare diseases biobanks and utilization of next-generation sequencing technology for the identification of novel causative variants and molecular diagnosis of rare disease patients. Responsible data sharing through the RD-Connect platform has been encouraged in order to promote also future discoveries.

Through its networking and training activities BBMRI-LPC has contributed to better integration of European biobanks; support of new biobank initiatives, particularly in the Eastern Europe; and global integration of biobanking and health organizations. The annual Biobank Forum meeting established within BBMRI-LPC has served as a communication platform for information exchange from countries with advanced population cohorts and registries to those that are planning to initiate large population-based biobanks. This successful concept has been agreed to be continued by BBMRI-ERIC.

BBMRI-LPC has made a key contribution towards advancing public-private interactions to enhance medical innovation. The BBMRI-ERIC Expert Centre concept was published as a novel model of non-profit, quality-controlled academic-industrial collaboration (van Ommen *et al* 2015). In a more recent follow-up paper, four Expert Centres have been described, two of them already recognized by BBMRI-ERIC. This paper is the first structured inventory of public-private collaborations of European biobanks and shows in a series of interviews how European biobanks are now engaging widely in such collaborations and consider establishing more Expert Centres or joining existing ones (Hämäläinen *et al*.; manuscript under review).

A strong scientific platform for evidence-based research on optimized sample handling and management has been established and there is a clear motivation to continue this work beyond BBMRI-LPC in close collaboration with BBMRI-ERIC Common Service IT and BBMRI-ERIC Quality Manager. Both the BRISQ database and the Common Catalogue for Biobank Services (CCBS) will be established as dynamic, web-based tools, which will have an impact on promoting both biobank quality and sustainability. Eventually, improved biobank quality is envisaged to stimulate the entire research community to seek access to the available biobank resources.

Biomarkers that can aid in disease diagnosis, especially at early stages, will have an important health impact by enabling therapeutic interventions at a stage when diseases may still be tractable. Advanced protein analysis technologies have been developed in the course of BBMRI-LPC, addressing the issues of sensitivity and throughput. Indeed, the equivalent of hundreds of thousands of individual diagnostic assays have been rapidly performed using the proximity ligation assay and protein array methods during the course of the BBMRI-LPC project. The modified proximity ligation assays can offer greatly increased sensitivity in the protein biomarker assays without need for specialized equipment. Such assays can translate to earlier detection of biomarkers that herald disease onset and thereby permit intervention before more extensive tissue damage. These assays are currently explored further by *Olink Proteomics*. To identify and validate discovered biomarkers, it will be necessary to expand further inexpensive analytic techniques for large-scale applications, and very large numbers of samples need to be collected. The latter is necessary so that a sufficient number of samples will be available from times when the diagnosis ought to be made, that is before any overt symptoms. The collection of dried blood samples developed within BBMRI-LPC provides an original and affordable means of archiving thousands of samples for protein analysis. Biomarker analysis will also require the collection of very large prospective cohorts, and collaborations between groups engaged in this work. There is also a need for specialist Expert Centres where samples can be analysed under standard conditions to allow results to be compared across many such centres. The BBMRI-LPC project has begun to address all these points by bringing together groups operating large prospective cohorts, individuals developing improved analytic techniques, and by considering novel forms of biobanks. The build-up of a series of Expert Centres can also harmonize analyses without the need to transport samples across national borders. In this manner, BBMRI-LPC has taken some important steps on a long journey towards improved disease management.

1.4.2. Main dissemination activities and exploitation of results

1.4.2.1. Dissemination activities

BBMRI-LPC partners have actively disseminated project outputs and research results to both scientific and general audiences, as demonstrated by the extensive list of dissemination activities summarized here and reported in more detail in the later section of this report (Table A2. List of Dissemination activities).

Research community

BBMRI-LPC representatives have made best efforts to disseminate research results to a wide scientific audience through publications in leading scientific journals, presenting information and project results at international conferences (Figure 5), meetings, workshops and courses, both external or co-organized as part of the BBMRI-LPC activities.

Figure 5. BBMRI-LPC posters presented at the Global Biobank Week 2017 in Stockholm, SE.

So far, BBMRI-LPC partners have published close to 70 articles or scientific papers related to the project activities, many in high-profile journals (Table 5). In addition to already published articles, there are several manuscripts under preparation to summarize essential BBMRI-LPC outputs and findings (Table 5). A list of publications related to the project activities and to the downstream research results generated by the access projects, will be maintained on the BBMRI-LPC project website and regularly updated.

A BBMRI-LPC catalogue has been developed to provide information to scientists about the resources available in participating cohorts. In addition, a catalogue of exposure variable and clinical endpoint data has been compiled. These catalogues are publicly available on-line on the project website (http://www.bbmri-lpc.org/) and BBMRI-LPC access portal (http://bbmri-lpc.iarc.fr/mica/). Also, the web-based access cost calculation tool, BBMRI-LPC cost calculator, will remain publicly accessible on-line at https://epi.helmholtz-muenchen.de/tools/calc/. The BRISQ database and the Common Catalogue for Biobank Services (CCBS) are being established as dynamic, web-based tools, promoting biobank quality and sustainability in collaboration with BBMRI-ERIC.

The BBMRI-LPC website (Figure 6) has been used for active dissemination of both BBMRI-LPC-related and general information on biobanking. As a special activity, the BBMRI-LPC Coordination Office has weekly or bi-weekly published a recommended *Biobanking article of the week,* highlighting the biobanking-related articles with interesting topics and pertinent questions (http://www.bbmri-lpc.org/node/46). The top 3 visited pages on the project website included the *Scientific calls, the European Biobank Forum* and the *Biobanking article of the week.*

The presence of BBMRI-LPC in the Social Media has been strong as shown by the number of followers in Twitter (n=265) and Facebook (n=151), many of which institutions. Links to BBMRI-LPC Facebook (https://www.facebook.com/bbmrilpc/) and Twitter (https://twitter.com/BBMRILPC) pages are provided at the project website.

Table 5. List of selected publications and article manuscripts under preparation related to the BBMRI-LPC project activities.

Title	Authors	Details
Connecting biobanks of large European cohorts (EU project BBMRI-LPC) [*in German*]	Kuhn K, Bild R, Anton G, Schuffenhauer S, Wichmann HE	*Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 2016; 59(3): 385-9
Public Biobanks: Calculation and Recovery of Costs	Clément B, Yuille M, Zatloukal K, Wichmann HE, Anton G, Parodi B *et al.*	*Science Translational Medicine* 2014; 6(261)
Maelstrom Research guidelines for rigorous retrospective data harmonization	Fortier I, Raina P, van den Heuvel ER, Griffith LE, Craig C, Saliba M *et al*.	*International Journal of Epidemiology* 2017; 46(1):103-115
Software Application Profile: Opal and Mica: open-source software solutions for epidemiological data management, harmonization and dissemination	Doiron D, Marcon Y, Fortier I, Burton P, Ferretti V	*International Journal of Epidemiology* 2017 (epub)
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Stability of proteins in dried blood spot biobanks	Björkesten J, Enroth S, Shen Q, Wik L, Hougaard DM, Cohen AS *et al.*	*Molecular Cellular Proteomics* 2017; 16: 1286-96.
Analytically sensitive protein detection in microtiter plates by proximity ligation with rolling circle amplification	Ebai T, Souza de Oliveira FM, Löf L, Wik L, Schweiger C, Landegren U *et al.*	*Clinical Chemistry* 2017; 63: 1497-1505
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Evaluation of the needs and challenges of harmonization of exposure data in the BBMRI-LPC project: A user's perspective [*In preparation*]	Illner AK, Slimani N *et. al*	Manuscript in preparation
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The BBMRI-LPC call to sequence 900 Rare Disease exomes: a successful transnational ollaborative initiative with EuroBioBank and RD-Connect [*In preparation*]	Beltran S, Gut I *et al*.	Manuscript in preparation
Quality assessment by metabolomics of serum and plasma samples from nine European biobanks [*In preparation*]	Abuja P, Anton G, Christiansen N, Gieger C, Ghini V, Zins M *et al.*	Manuscript in preparation

Emerging biobanks

The BBMRI-LPC Forum has created an information exchange platform between established and emerging large-scale biobanks and will be continued by BBMRI-ERIC. Several international workshops and courses on practical biobanking directed towards emerging biobank countries were organized. Several local training events, workshops and exhibitions on biobanking were organized also nationally by the BBMRI-LPC-participating institutes.

The BBMRI-LPC website (Figure 6) was used for active dissemination of various biobanking-related information and material directed towards the emerging biobanks. Presentations of the previous BBMRI-LPC training events are available on the project website. A *Handbook of Practical Biobanking* containing useful information on biobanking-related strategies, guidelines, publications, presentations and white papers is accessible on the internal area of project website. A *BBMRI-LPC Biobanking Helpdesk* has enabled sending questions to be submitted to the BBMRI-LPC experts through an on-line web form accessible on the project website.

General public

Taken its complex and multifaceted nature, BBMRI-LPC may have remained a bit obscure to the wider audience of the general public. Nevertheless, the project website has also been used as a channel for disseminating the more basic concepts of the project which may have been of interest also to the public as a whole.

Figure 6. Screenshot of the front page of the BBMRI-LPC website (http://bbmri-lpc.org/)

1.4.2.2. Exploitation of results

The biobanking and scientific community is one of the primary users to take up the ample experience and knowledge gained from different BBMRI-LPC activities for further exploration and use in improving the access provision process and harmonization of various biobanking-related procedures. Several concepts and solutions developed during the course of BBMRI-LPC are in the process of being sustainably integrated with the BBMRI-ERIC activities.

The downstream results obtained from the access research projects will advance the general knowledge of the studied conditions. Different tools developed during BBMRI-LPC, such as BBMRI-LPC catalogue, BBMRI-LPC cost calculator, and Common Catalogue for Biobanking Services, are envisaged for exploitation by the biobanking community.

The advanced methods for protein analyses based on antibody-DNA conjugates and protein microarrays developed during BBMRI-LPC will greatly benefit research on disease mechanisms and diagnostics as well as development of potentially predictive or preventive clinical biomarkers. Some of these methods (such as proximity ligation assays with rolling circle amplification) also represent targets for commercial exploitation.

1.5 Address of the public project website and contact details

Website: http://bbmri-lpc.org/
Email: info-bbmrilpc@helsinki.fi

Contact details:
Professor Markus Perola
Institute for Molecular Medicine Finland (FIMM)
HiLIFE unit, University of Helsinki
Biomedicum Helsinki 2U
Tukholmankatu 8
P.O. Box 20
FI-00014 University of Helsinki
Finland