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A website on nutrition and cancer – patients perspective

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Rationale
One of the most consisting findings in health services research is that scientific knowledge is often not used in the routine care of patients resulting in inefficient, inappropriate or even harmful care. Therefore, a website was developed to make evidence and eminence-based information on nutrition and cancer available to the general public, to cancer patients and cancer survivors, which makes the website a unique concept. The aim of this study was to evaluate the use of this website.

Methods
A pre-test in cancer patients and healthcare professionals was performed to evaluate whether the website fits the target group. Focus groups with cancer patients were organized to identify patients’ information needs regarding nutrition and cancer and to explore whether the website suits these needs. After launching the website, questions of visitors of the website were collected and answered by dieticians and nutritional scientists. Once the website was online, question categories and website statistics were recorded.

Results
After the pre-test, key areas for improvement like navigation, categorization and missing information were identified and adjusted. Results of the focus group showed that main patients’ needs were on nutrition during treatment and trustworthy information in general and that those needs were met by the website. In the first fourteen months after the launch the website was visited 120,093 times, with 150 visits a day at the start up to 560 a day at this moment. A total of 335 questions was submitted on nutrition and cancer. Most questions were on prevention of cancer and nutrition during the treatment of cancer.

Conclusion
As can be concluded from the number of questions submitted and the number of visitors to the website, the new website with evidence and eminence-based information on nutrition and cancer fills a gap on the internet.
The donor as partner: engaging patients and publics in biobank governance

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Background
Achieving and sustaining public trust, political support and societal relevance are crucial for the long-term success of biobanking. Engaging citizens and patients in biobank governance is vital to achieving those objectives. This project provides guidance to those involved in managing and governing biobanking as to how they might do so legitimately, effectively and efficiently.

Methods
Based on a literature review of engagement in biomedical research, a qualitative assessment and survey of ordinary engagement practice in Dutch biobanking, as well as a number of case studies of best practices worldwide, a report was drawn up. Recommendations were subsequently validated through focus groups with experts and stakeholders involved in biobanking, public policy, participation research and patient organizations.

Results
The guideline helps assess the needs for and feasibility of engagement by providing a step-by-step approach to (1) the potential themes for engagement in research objectives, procurement practice and public support; (2) the extent to which engagement has been taken into account in biobanks’ governance frameworks and policies; (3) the space, scope and broader needs for engagement on the remaining issues. The report, available for download here, provides practical guidance as well as an accessible collection of case studies of engagement in biobanking.

Discussion
Currently, BBMRI-NL 2.0 is following up on these recommendations through its ELSI Centre of Expertise by providing consultation services on and setting up thematic projects involving engagement to biobanks, researchers and patient organizations. Progress updates can be found at BBMRI.NL.
Current DNA sequencing platforms can analyze tens of thousands individual genomes per year, enabling large-scale population genetics. Detection of sequence variants is ideally performed in the context of the entire cohort, begging for thousands of samples to be analyzed in parallel. This is a computational and bandwidth challenge due to the huge amount of data that needs to be processed.

The validation results of the novel GENALICE MAP Population Calling module, which is an extension of the GENALICE MAP NGS data analysis suite, are being presented. It is a fully scalable module that adds individual samples to a larger cohort using an incremental approach. Its processing speed is more than two orders of magnitude faster than GATK's joint genotyping method. Compared to single sample variant detection, the Population Calling module has improved variant detection accuracy. The resulting variant calls are stored in a novel format, called GENALICE Variant Map, allowing fast data access and retrieval, which will be crucial for cohorts consisting of thousands of samples.

The Population Calling module operates with a fully linear scalability. Given its low computational requirements and high processing speeds per genome, the GENALICE MAP Population Calling module is a highly time and cost-effective manner to detect sequence variants in large cohorts.
HIT CF; patient participation in an outstanding scientific research program
A close cooperation between patients representatives, clinicians, and researchers as equal partners; description of a breakthrough research program aiming towards precision medicine in Cystic Fibrosis

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A close and effective collaboration between clinicians, researchers and patients representatives can ultimately lead to a research program that is targeting the needs of patients, as prioritized by themselves. The role of the patients representatives in developing, executing and funding the program is crucial; this kind of patients participation is defined as institutionalized patients participation. Through close cooperation between the Dutch Cystic Fibrosis Foundation (NCFS), clinicians and researchers, a scientific research program was defined, called “HIT CF”. It is consisting of 4 tracks with 16 projects with a budget summing up to € 4.5 million.

The HIT CF program aims to establish a breakthrough in CF treatment through further development of compounds that effectively modify basic disease mechanisms, combined with innovative ways to test drug efficacy in individual patients. The programme will ultimately lead to a laboratory setting in which the efficacy of drugs can be predicted in individual patients, which will enable precision medicine by targeting the treatment (or combination of treatments) to the most responsive patients. HIT CF is running for 3 years now and the program has already enabled the selection of individuals for novel CF treatments, demonstrating proof of principle for precision medicine in CF.
Individualized dosing of anti-thymocyte globulin in pediatric hematopoietic cell transplantation to improve outcome - A clinical, pharmacological, and immunological collaboration towards personalized medicine

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Introduction
Hematopoietic cell transplantation (HCT) is a curative treatment for diseases including leukemia, immune deficiencies and metabolic disorders. However, mortality of this procedure is ±30%, mainly due to relapse of malignancy, viral reactivations, and graft-versus-host-disease (GvHD). Anti-Thymocyte Globulin (ATG) is used to prevent GvHD and rejection by \textit{in-vivo} depletions of T-cells. Over-exposure by ATG however leads to delayed or absent immune reconstitution (IR), possibly leading to relapse or viral reactivations. Previous research investigating pharmacokinetics (PK) and pharmacodynamics (PD) of ATG indicated a strong association between ATG exposure and IR, while IR (and ATG exposure in subgroups) was a determinant of overall survival (OS). Here, we calculate individual dose of ATG aiming for target exposure to increase outcome of HCT.

Methods
From 2014, all pediatric patients receiving a HCT in the University Medical Center Utrecht were given individualized ATG dosing with added therapeutic drug monitoring (TDM) for those at high risk for rejection. From July 2015, patients were included in a prospective study. Dosing is based on body weight and peripheral blood lymphocyte counts (determining PK) and stem cell source (determining PD). For TDM-patients, in addition to individualized dosing, dose was adjusted based on individual pharmacokinetics. Dosing was calculated using a Linux-based application integrating R and NONMEM.

Results
13 patients have been treated according to this protocol, of which 5 received TDM. The application was easy to use. In all TDM-patients, actual exposure was within the target. Median follow up is 199 days. Immune reconstitution was significantly improved when compared to historical controls, and comparable to patients not receiving ATG. No rejection occurred, 1 patient had mild GvHD. Encouraging survival rates of 89\%±10\% were observed.

Conclusion
Optimal ATG dosing is pivotal for predictable immune reconstitution, potentially leading to improved outcome following pediatric HCT. With the developed framework, individualized dosing is possible, taking into account patient characteristics and optimal ATG exposure. We will facilitate the implementation of individualized dosing by developing an application, either for smartphone or web-based, to enable multi-center use of this computational dosing calculation model.
Patient Innovation Corner

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In implementation and innovation of personalized medicine, the ideas of patients with regards to improving care are essential to fit health care to the patients’ perspective. Moreover, enhancing the collaboration between patients and different professionals is of importance in enabling personalized medicine.

To facilitate collaboration between patients and professionals, a Patient Innovation Corner will be created at the Radboudumc, an Academic Medical Center in Nijmegen, the Netherlands. In the Patient Innovation Corner, patients meet with students of different studies, care professionals and researchers to discuss their ideas with regards to improving care, during their visit to the hospital.

By combining the innovative ideas for improving care of patients with the skills and expertise of (upcoming) care professionals and researchers, potential winning solutions in improving personalized medicine and person-centered care will be worked out from the idea-phase to implementation and examination of effectuation.

Students of different studies from the Radboudumc and Radboud University play an essential role in working out the ideas to a realistic and implementable solution in collaboration with patients. Moreover, by collaborating with researchers of the academia in Nijmegen, there is a vehicle to examine the effects of innovative patient solutions.

The Patient Innovation Corner provides the patient with a platform to talk about improvement of care and enables patients to make a contribution to improving personalized medicine at the Radboudumc, by working together with students, care professionals and researchers.

The Patient Innovation Corner facilitates patients, students and professionals to meet and collaborate to improve and innovate healthcare practice and policy.
Public-private partnerships in clinical cancer research: a case-study on the Screening Patients for Efficient Clinical Trial Access (SPECTA) of the European Organization for Research and Treatment of Cancer (EORTC)

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Precision medicines (PM) target specific molecular alterations and are thus only useful for subsets of patients. To translate the promising opportunities of pharmacogenomics, researchers from the profit and non-profit sector should have access to high-quality bio-specimens and associated data entailing information to understand diseases, to discover new biomarkers and develop innovative medicines and diagnostics. The purpose is to describe how different biobank initiatives in cancer research deal with public-private partnering. In particular it investigates partnership approaches around a novel model of biobanking: ‘collaborative molecular screening platform’ (CMSP). A case-study is performed on the Screening Patients for Efficient Clinical Trial Access (SPECTA) platform, proposed by the European Organization for Research and Treatment of Cancer (EORTC). Independently of a specific protocol, SPECTA screens and sorts patient based on molecular alterations and facilitates data access. Besides optimized patient access and considerable savings in time and costs for industrial partners and researchers, such initiative facilitates access to real-world data as input for early economic evaluations for health technology assessments. Moreover, such real-life database is becoming increasingly important for regulators in post-approval phases with Adaptive Pathways under discussion. A research study addresses how CMSPs can be framed in a broad stakeholder network by using qualitative and quantitative methodologies. First, stakeholder’s views are identified and used to model collaborative scenarios. It is proposed that CMSP could have a pivotal role leveraging the clinical deployment of PM.
The central role of the power-user to connect translational research to translational research IT infrastructure

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In translational research all projects basically share the same intention, which is correlating variations in disease phenotype to variations in underlying biology. Over the years, different research laboratories have generated large amounts of (experimental molecular) data from patient samples, however, generally this information is inaccessible for examination due to local storage of both (meta)data and the data processing workflows that were used. Alternatively, data stored in central databases may only be available for exploration and interpretation by data specialists, provided that the processing workflow has been published and is available. This difficulty in accessing and examining previously generated data often leads to researchers setting up new experiments, or even re-doing them, while answers could have been derived from already existing data.

One of the major issues here is that, currently, there are no definite standards on how to sustainably manage research (meta)data for the different data types; and this problem is something that the Translational Research IT (TraIT) project, initiated by the Center for Translational Molecular Medicine (CTMM), aims to provide end-to-end solutions for. As not all data can be suitably accommodated in just one tool, a variety of tools has been selected in TraIT to accommodate clinical, (bio-)medical/ pathological imaging, biobank and experimental (meta)data. Of each of these domains the processed, ‘final’ data may become available on a data-integration platform for viewing, querying and analysis.

To determine whether the chosen tools were indeed suitable for the different types of research (meta)data I was hired at the beginning of TraIT as a power-user. Coming from a translational research setting I had encountered the same issues related to examining (publically) available data and sustainable management of generated data. In TraIT I represent the general researcher who has little to no (bio-)informatical experience, but whom would like to investigate multiple (experimental) data types without having to become an expert in each research domain. Therefore I tested a variety of tools for functionality and user friendliness in storing the experimental (meta)data, as well as their capability of allowing me to run analysis pipelines within both the domain specific tools as well as the data-integration platform. As a member of the Foundation team, feedback for adaptation and further development of the tools was given through weekly (sometimes daily) iterative interactions with IT developers from Philips and the Hyve; by explaining how and why a researcher would want a certain adaptation or new functionality. Collaboration with experts from various research domains (Erasmus University Medical Center, Maastricht University, University Medical Center Groningen, Netherlands Cancer Institute, VU University medical center and TNO Quality of Life) and sharing of knowledge on a variety of experimental platform data-formats and associated processing pipelines was essential to expand upon the functionality of TraIT tools and to encompass solutions for more data-types. Each time, new developments were tested in order to check their correct implementation and if necessary, bug reports were filed or further development was planned to get the tools working optimally.
By now, TraIT offers a variety of tools to researchers to sustainably manage their data. Having obtained insight into the limitations and capabilities of the various tools, I now take part in data consultancy for researchers who would like to start using the solutions offered by TraIT and provide training and support for some of these tools. Lastly, I am also a member of the data-team, which is tasked with getting the processed or ‘final’ data of TraIT customers onto the data-integration platform for easy view and query. Coming round to end-to-end solutions; from this platform researchers will also be able to trace back the original raw data and processing pipelines used to obtain this ‘final’ data, and link out to other environments for further (customised) viewing, querying, processing and analysis.
Rare lung disease biobank and research, the importance of collaboration with patient associations and (inter)national networks

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Interstitial Lung Diseases (ILD) are rare diseases, of which causes are often unknown and there is no curative treatment for many of these diseases. In the St. Antonius ILD Center of Excellence, Nieuwegein, The Netherlands, a biobank was founded ten years ago for research purposes. With the research conducted on biobank materials we aim to obtain a better understanding of cause and course of disease, to ultimately improve care and prognosis and possibly prevent ILD. Currently, over 4500 patients with ILD are included in the ILD biobank.

Biobanking rare diseases requires nationwide adherence to reach sufficient numbers of patients. To reach patient for biobank participation, in-house and out-house protocols were developed. In-house protocols reach the patients visiting our outpatient clinic and ask for participation during their first visit. Out-house protocols enable participation of patients from other hospitals nation-wide. To attain national exposure, collaboration was entered with several patient associations. They inform their patients in their magazines, newsletters, and websites about the possibility to participate in the biobank. Another advantage of collaboration with patient associations, is to inform their members during patient meetings on latest developments in research. Furthermore, we make use of a national network with pulmonologists in other hospitals that was established for ILD shared-care constructions. These pulmonologists can inform their patients about the ILD biobank.

Research on rare disease is international by nature. The ILD Center of Excellence is a partner in international networks, i.e. the international LAM Clinics Network and the European PAP network. These networks organize conference calls in which latest knowledge is shared and international trials are promoted, for example.

To summarize, collaboration in rare disease research with other, non-scientific partners, is essential to assemble patients for scientific research, such as clinical trials, retrospective and prospective studies, and to inform patients about their disease and latest developments in a non-clinical setting.
Privacy protection in cohort studies - The LifeLines solution

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Background
LifeLines is a prospective population-based cohort study and biobank that will follow 167,229 individuals for at least 30 years in the northern part of the Netherlands in a three generation design. High quality data, by means of physical examinations, questionnaires and analysis of biomaterial, are collected to push forward research on ‘Healthy Ageing’. Also, linkage is being established with medical registries, national registry data and environmental exposures. Privacy protection of participants is essential, because the dataset contains sensitive information. The aim of LifeLines is to be a resource for the national and international scientific community for research on Healthy Ageing. The data and biomaterial are available for researchers worldwide. In combination with the intention of LifeLines to maximally protect the privacy of the participants, this aim is challenging and asks for novel solutions in ICT and data access procedures.

Methods
When the data are processed for data release, the dataset is stripped from all personal details to prevent (in-)direct identification (pseudonimized) and is moved to a new database in a separate geographic location. Even after this procedure re-identification is possible, in particular after linkage with other data sources. We consider the level of possible re-identification in each dataset by assessing the level of uniqueness of subjects in each dataset using k-anonymity analysis. Based on the outcomes of this analysis, the aggregation level of the variables that contribute to the re-identification are adjusted. Each researcher gets access to a tailor-made dataset with only those data that are specifically needed to answer the research question. The data are made available for researchers by means of a private virtual environment: the LifeLines workspace.

Results
The adjusted aggregation level are implemented in each data release. A survey is being conducted among researchers to investigate the impact of this aggregation on scientific findings.

Conclusion
LifeLines has developed an innovative ICT and data management solution based on adjustment of the aggregation level of data provided to researchers. This can be implemented in other biobank and cohort studies.
3D Glioma-on-a-chip models for personalized medicine in OrganoPlates™

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Mimetas’ OrganoPlates™ are microfluidics-based 3D culture plates supporting culture and screening of a broad range of organ and tissue models. Here we describe the development of a perfused organotypic human glioma model, ultimately aiming for personalized therapy selection. In collaboration with the Department of Neurosurgery of the ErasmusMC and funded by the glioma patient foundation STOPhersentumoren.nl, Mimetas develops an organotypic glioma model in OrganoPlates™ to establish screenable cellular models for all glioma patients. Treatment of gliomas is complicated by variable response rates of individual patients’ tumors to therapies. ErasmusMC has developed a 2D culture platform (GLIOscreen) for screening patient-derived glioma tissues with potential therapeutic compounds. Unfortunately, not all patient-derived glioma tissues are amenable to 2D culture, probably caused by tumor heterogeneity, raising the necessity for additional, complementing culture models.

The OrganoPlate™ is a high throughput microfluidic platform enabling 3D cell culture, with a range of flow conditions and co-culture options (e.g. blood vessels), creating physiologically relevant models with a minimal requirement of cell material. The 3D cell culture conditions in the 2-lane OrganoPlate™ were optimized using the GLIOscreen-derived cell line GS365. A range of seeding concentrations and ECM’s (ExtraCellular Matrix) were tested and analyzed with a fluorescent live/dead assay. No difference in viability was observed between the various conditions. As BME2rgf-coated plastic is used for the 2D GLIOscreen, the BME2rgf was selected to grow cells in 3D in the OrganoPlate™. Freshly isolated tumor material (EGT141) seeded directly in 3D in a 2-lane OrganoPlate™ displayed high viability after 13 days of culture.

Temozolomide (TMZ) is the first line therapy in glioma treatment. To compare 3D OrganoPlate™ glioma sensitivity with results obtained in the GLIOscreen, the response to TMZ was analyzed with a fluorescent viability assay. TMZ sensitivity is determined by the methylation status of the MGMT promotor. MGMT can counteract the activity of TMZ, leaving cells less sensitive. The TMZ-sensitive GLIOscreen-derived cell lines GS203 and GS261 display a dose-dependent drop in viability in both 2D and 3D culture, however, 3D culture shows a markedly lower sensitivity. TMZ is a DNA-modifying anti-cancer drug and therefore primarily targets proliferating cells. As the proliferation rate of the glioma cells drops in 3D this would explain the lower sensitivity. Whether the culture of glioma cells in 3D better mimics the in vivo response remains to be validated. The strong interaction between the Erasmus Medical Centre and Mimetas, supported by STOPhersentumore.nl, creates the perfect environment for the validation of this organotypic glioma model.

In those cases of patients with oncologic diseases where there is no clear relationship between genomic profile and treatment, as is the case with glioblastomas, two aspects are of utmost importance: 1) representative tumor models to find such relationships and 2) representative tumor models that support therapy selection in vitro drug testing. The high-throughput OrganoPlate™ platform offers an attractive method for 3D culture of (freshly isolated) patient-derived glioma material, supporting development of individual tumor models for personalized selection of therapeutic compounds.
Education as a means to unite stakeholders in personalized healthcare

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The mission of the Radboud Umc is to have a significant impact on healthcare through, among others, personalized healthcare. One of the bottlenecks in the field of personalized healthcare is that the various stakeholders all speak a different language. We, as researchers and lecturers in a clinical setting, felt that education is warranted to improve the communication among the groups involved. Therefore, we developed a minor entitled “Novel Therapeutics in Personalized Healthcare” for Bachelor Biomedical Sciences and Medicine students, in which the former represent the future researchers and the latter the future clinicians.

The students focus on three different diseases, i.e. lung cancer, chronic pain and rheumatoid arthritis, and their targeted therapies. This minor aims at translating basic knowledge of signal transduction processes and molecular targets to drug design and challenges in clinical practice, including personal (genome, biomarkers) and societal matters (valorisation, personalized health). The latter aspect forms a common theme throughout the minor in the form of monthly contacts with patients.

In order to successfully complete this course, Medicine students will need to obtain additional insight in molecular pathways, and Biomedical Sciences students will need to deepen their knowledge of clinical problems. Importantly, the students themselves can teach each other these aspects in small groups guided by clinicians and researchers, thereby stimulating translational medicine even more profoundly.

In addition to professionals from the clinic and the lab, representatives of the pharmaceutical industry and the patient advisory board are responsible for specific parts of this course. The minor culminates in a debate and research proposal that will challenge the students to contribute to the issues of novel therapeutics in personalized healthcare from a molecular and a patient’s point of view, taking ethical matters ranging from healthcare costs to quality of life into account. As such, we believe that this minor aids in improving the communication between (future) stakeholders in the field of personalized healthcare.
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Lygature: Driving partnerships from idea to success - Pioneering medicine. Together.

J. Janssen¹

¹Lygature - CTMM and TI Pharma are merging and will be named Lygature as of January 1st, 2016.
www.lygature.org, info@lygature.org

Lygature drives the development of new medical solutions for patients by managing public-private partnerships that bring together academia, industry and society. Every day we pioneer solutions in the areas of medical technology and pharmacotherapy to serve patients worldwide.

Lygature is a not-for-profit organization based in the Netherlands. We build upon the legacy of the Center for Translational Molecular Medicine (CTMM) and Top Institute Pharma (TI Pharma).
Making translational research work - An easy-to-access and easy-to-use infrastructure for sharing and exploring research data

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“When you deploy TraIT in your research, your research data is securely stored in the cloud, allowing you to share it with other researchers and accelerate time-to-results without losing ownership.”

More than 215 studies and over 1,955 researchers as of October 2015 make use of the TraIT infrastructure, from small local investigator-initiated studies to multi-centre international programmes.

TraIT provides the Dutch hub in international networks and closely collaborates with initiatives like BBMRI, IMI-funded projects, ELIXIR and EATRIS.
Promoting use of biobanks through increased visibility of collections in biobank catalogues and directories

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Background
Biobanks are an important resource for biomedical research and contain large collections of biological samples and accompanying clinical data. So far biobanks have been underutilized because it is often difficult for researchers to find the collections that have relevant samples and data. To promote the discoverability and use of biobanks we have developed easy to access and query catalogues of the biobanks and their collections.

Material & Methods
Different levels of catalogues have been developed in the different biobank catalogue work packages or working groups ranging from only summaries per collection down to per-sample information. We used MIABIS as a common minimal information model to describe biobanks and collections in the different projects and we used MOLGENIS open source software to allow rapid development/configuration of new catalogue websites in a standardized and modular way (http://github.com/molgenis/molgenis).

Results
Within the different projects we have identified the biobanks that are of interest to the project and published these in a biobank catalogue or directory, including BBMRI-NL, BBMRI-ERIC, CTMM TraIT biobank catalogue, RD-Connect sample catalogue, PALGA open database, LifeLines data catalogue. To enable data sharing, between the BBMRI-NL catalogue and the BBMRI-ERIC directory we established a data exchange so the biobanks can be found at both the national and the ERIC level with just a single data entry. In the BBMRI-NL catalogue almost 200 biobanks are listed, while the BBMRI-ERIC directory lists over 500 biobanks.

Discussion
Further development of the software should address open issues to improve accessibility of the biobanks, and further integrate their data. Semantic search could enable relating collections that have similar data, but use different code systems (e.g. SNOMED-CT vs. ICD-10). A federative querying model will allow more in-depth searches of the biobank data, while leaving the biobank in control of potentially sensitive data. Find examples at https://catalogue.bbmri.nl http://www.palgaopenbaredatabank.nl/ https://catalogue.lifelines.nl http://directory-molgenis.bbmri-eric.eu/
Towards global biobank integration by community review and implementation of minimum information about biobank data sharing (MIABIS) 2.0

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Background
Research into complex and rare diseases requires high quality biological samples. However, it is costly and time consuming to create novel sample collections of appropriate size and quality. At the same time biobanks have large collections that are underutilized, because discoverability and access to the samples is hard. Several catalogues have been published to facilitate the use of biobanks in research, but these are often incomplete, incomparable and outdated. A working group was formed within BBMRI-ERIC in order to update MIABIS to facilitate the exchange of information between biobanks, national nodes, consortia and research groups using biological samples.

Material & Methods
The working group has revisited the MIABIS recommendation made it more flexible:

- The model has been split in core components: biobanks, sample collections, and studies, and supporting components: sample, participant, omics and rare diseases;
- The number of elements has been reduced;
- Data structures have been defined for several elements.

Results
The MIABIS 2.0 model has been successfully implemented using MOLGENIS in BBMRI-NL, BBMRI-ERIC and RD-Connect and various other software in the BBMRI National Nodes, BiobankCloud, EUDAT, BioMedBridges and IARC.

Discussion
A minimal information model enables interoperability between different systems. MIABIS facilitates automated exchange of information between several systems in the biobanking workflow such as Biobank Information Systems, Catalogues and Workflows for sample request and access. However, other components are needed to unlock the full potential such as Standardization of terms in ontologies and Globally unique identifiers such as BRIF for biobanks, samples collections and samples.

Participate in MIABIS development at https://github.com/MIABIS/miabis/wiki
The Dutch National Tissuebank Portal - One portal to all pathology archives

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Objective
The Dutch National Tissuebank Portal (DNTP) project aims to achieve increased, easier and improved secondary use of residual human tissue samples (FFPE blocks) from all pathology laboratories in the Netherlands.

Method
The DNTP works closely with PALGA. PALGA is the nationwide network and virtual registry of histo- and cytopathology in the Netherlands. All 50 hospitals with a pathology laboratory are connected to the central PALGA database. Currently, there are 60 million archived FFPE samples with standardized associated data in these hospitals which can be used for research purposes. With the DNTP portal researchers can request samples online from where it will automatically be sent to the pathology laboratory where the samples are stored. After approval from a research- and privacy committee and the participating laboratory a DNTP employee will collect the samples and send them to the researcher. Pathology laboratories can request a sample to return, if this sample is needed for delayed patient care.

Results
The result will be that in the Netherlands we have established a professional research infrastructure that will provide virtual and physical access to all residual FFPE pathology samples and their associated data for research purposes. Nowhere in the world does such a web based portal exist that supports pathology laboratories and researchers in their quest of searching, requesting, registering, retrieving and returning archived FFPE samples for research from all the national pathology archives.

Conclusion
This project was financially supported by Biobanking and Biomolecular Research Infrastructure The Netherlands (BBMRI-NL), a research infrastructure financed by the Dutch Government (NOW 184.021.007). BBMRI-NL co-ordinated the collaboration between Dutch biobanks. It is not a biobank itself, but facilitates collaboration by harmonization and enrichment of existing biobanks.
Nationwide online ExpertPanel to improve tailored treatment of pancreatic cancer

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Introduction
Anually, 2300 patients are diagnosed with pancreatic cancer in the Netherlands.¹ Only 20% of the patients are eligible for a potentially curative resection. Due to the centralisation of pancreatic cancer treatment in the Netherlands the quality and safety is improving but knowledge and implementation of new therapies and techniques (e.g. induction chemotherapy making initially unresectable disease ultimately resectable) are also increasingly limited to these centers²,³. This phenomenon could lead to a “pancreatic brain drain” in smaller centers. The Dutch Pancreatic Cancer Group (DPCG) aimed to develop an online DPCG-ExpertPanel to facilitate and tailor rapid expert advice for patients with pancreatic cancer.

Patients & Methods
In collaboration with Aexist (The Hague, the Netherlands) we developed the ImageHub® system which allows for secure, online review of CT scans. Next, we installed a nationwide multidisciplinary DPCG-ExpertPanel for pancreatic cancer. This is a nationwide prospective analyses of the first patients diagnosed with pancreatic or peri-ampullary cancer who were referred to the online DPCG-ExpertPanel between June and October 2015.

Results
A total of 34 patients from 12 centers were referred to the online DPCG-ExpertPanel and in 53% (18/34) of the patients this led to a change in treatment strategy. Resection with curative intention was advised in 2 patients (6%) and 16 patients were eligible for trial participation. In all cases the DPCG-ExpertPanel advice was provided within 5 working days.

Conclusion
The DPCG has successfully installed an online ExpertPanel for pancreatic cancer with the ImageHub® system. This DPCG-ExpertPanel is feasible and provides expert advice within an acceptable period of time. The next step will be a regional implementation project to further evaluate the validity of this system.

References
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Context-specific regulatory effects of genetic risk factors

P. Deelen

1The BIOS consortium

Using 2,000 population-based RNA-sequencing samples, we find that 22,919 genes are under control of genetic variants (eQTLs). Half of these genes are under control of multiple independent genetic variants. 1,583 of the regulatory variants are in strong LD with disease associated variants, this allows us to link a large proportion of known disease associated variants to affected genes. Additionally we are also able to show if the gene is up regulated or down regulated in individual’s carrying the risk allele.

We also observed that higher order effects induce, abrogate, or inverse eQTLs. Using gene-expression levels as proxies for stimulations, we were able to identify regulatory effects that are dependent on different conditions and stimulations. This allowed us to detect, among others, erythrocyte and natural killer dependent regulation but also effects that appear to be drive by type 1 interferon. We are able to replicate known eQTL modifiers, for instance the previously identified rhinovirus dependent eQTLs (Çalışkan, et al., PLOS Genetics, 2013).

These findings help to further improve interpretation of disease-associated variation. For Inflammatory bowel disease (IBD) for instance, we find that for some of the risk variants the regulatory function is mainly active within in neutrophils and others in natural killer cells of CD4+ T-cells. These cell types are known to be of importance in IBD and now we can link specific variants and genes to these cell types aiding follow-up investigations.

In conclusion, we observed numerous examples where genetic risk factors affect gene expression only in a specific context. Since it is not feasible to collect eQTL data for all tissues and cell-types in combinations with all potential stimulations and cellular states, approaches that can untangle the effects of different stimulations and cell types from tissue data are essential to properly interpret the effect of regulatory genetic variation.

The BIOS project is funded by the BBMRI-NL, a research infrastructure financed by the Netherlands Organization for Scientific Research (NWO project 184.021.007).
The Ethics of Organoids: perspectives of patients with Cystic Fibrosis (CF) - A qualitative interview study

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Organoid technology is an emerging new research area and is expected to contribute to the fields of precision medicine and regenerative medicine. Organoids can be made out of stem cells and are complex three-dimensional chunks of cells or ‘mini-organs’ that resemble the architecture and function of real-life human tissue. Organoids can replicate and expand indefinitely and can be stored in ‘Living Biobanks’ for unlimited time.

One such application in the realm of precision medicine is research that is conducted in the field of Cystic Fibrosis (CF). CF is caused by a mutation in the CFTR-gene. Traditionally, treatment has been mainly symptomatic. Nowadays, however, drugs are being developed that target mutation-specific defects of the CFTR-protein. The potential of organoids as an in-vitro model to test individual drug response, drug efficacy and novel drugs is being investigated. Currently, patients with CF are enrolled to donate intestinal tissue for the derivation of disease specific organoids. This research was initiated by the Dutch Cystic Fibrosis Foundation (NCFS) and the Wilhelmina Children’s Hospital in Utrecht and forms part of a broader project, entitled “HIT CF”.

Organoid technology is a promising field. However, it also brings about several ethical challenges. The convergence of developments like stem cell research, genomics and biobanking that led to organoid technology, combined with the commercial and clinical potential, give a specific twist to ongoing ethical debates. In an earlier paper (Boers et al., 2015, under review) we identified four ethical themes that deserve further examination. First, the moral and legal status of organoids should be explored. Second, organoid technology will face many consent challenges and an emphasis on consent alone may not provide sufficient moral justification. Third, the concept of mixed models in biobanking requires distinct governance structures. Fourth, ethical challenges related to first-in-human complex translational trials should be anticipated.

We consider it of great importance to conduct ethical parallel research and to co-create organoid technology together with researchers, clinicians, donors and future users. Therefore, we initiated a collaboration with the Dutch Cystic Fibrosis Foundation (NCFS) and the Wilhelmina Children’s Hospital. We aim to examine the perspective of patients with CF regarding organoid technology, because they are involved in several pivotal stages: they are the donors and the end-users. Accordingly, we conduct qualitative semi-structured interviews with patients with CF and their parents.
SURF for life science and health research

I. Nooren\textsuperscript{1}

\textsuperscript{1}SURFsara

Due to the very data-intensive nature of Life Science and Health research, the research community faces a rapidly growing need for suitable ICT services, ICT support and training. As a cooperation of Dutch academic medical centers and universities for ICT services and innovation, SURF (SURFsara, SURFnet, SURFmarket) develops and provides national ICT facilities that are tuned to the needs of the research community. SURF closely collaborates with national projects like CTTM-TraIT, BBMRI and NFU Data4LifeSciences to innovate on authentication, data sharing and storage, computing and online collaboration. Currently, more than 400 TB of research data and 15 million core hours per year are used for data storage and analyzed at SURF facilities. This shows that SURF operates at the heart of ICT innovation and research to facilitate researchers to compete with colleagues world-wide. The joint effort in ICT innovation provides opportunities to enhance the development of personalized medicine.
Systematic identification of downstream trans-effects for 1,900 known disease associated SNPs

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* BIOS stands for Biobank-based Integrative Omics Study, a BBMRI-NL Rainbow project steered by Lude Franke (UMCG), Bas Heijmans (Chair, LUMC), Peter-Bram ’t Hoen (LUMC), Aaron Isaacs (EMC) Rick Jansen (VU), and Joyce van Meurs (EMC)

Genetic risk factors identified in genome-wide association studies are mostly non-coding, making it difficult to understand their functional consequences. So far, large-scale trans-eQTL analyses have identified such downstream functional consequences for only 233 SNPs (Westra et al, NG 2013). To increase this, we used methylation-QTL mapping in peripheral blood of 4,000 population based samples from the Dutch BBMRI-NL BIOS consortium. We observed that 1,907 different GWAS SNPs affect methylation of over 10.141 unique CpGs sites in trans (FDR <0.05), representing an eight-fold increase in the number of disease-associated SNPs for which downstream functional effects can be detected.

To address the question in what particular biological processes these specific CpGs are involved, we also generated RNA sequencing data for 2,000 of the samples, permitting us to empirically relate CpG methylation to gene expression effects (eQTMs) for over 12,800 CpG sites (FDR <0.05). By using different genomic annotations we could accurately predict (AUC = 0.83) whether these methylation-gene expression relationships were positive (31%) or negative (69%).

By finally integrating the trans-meQTLs and eQTMs and adapting pathway enrichment method DEPICT, we obtained insights in the downstream functional effects of many genetic risk factors: rs3774959 (mapping close to NFKB1 and associated with ulcerative colitis) significantly affects methylation levels of 348 different CpG sites, of which many map within genes of the NF-kappaB cascade.

These results indicate that large-scale meQTL mapping permits discovery of previously unknown downstream molecular effects for many genetic risk factors, and these effects on trans- methylation levels have a clear biological basis.
Multi-omics data analysis in tranSMART using the Cell Line Use Case dataset

W. Weistra

1The Hyve, CTMM TraIT

Abstract
With the establishment of next generation sequencing and the advent of proteomics and metabolomics in the translational research domain, there is an increasing need for integrating different multi-omics datasets. In the course of different recent projects, The Hyve has developed new multi-omics capabilities for the translational research platform tranSMART (http://transmartfoundation.org/). In addition to clinical (low dimensional) data and mRNA expression data, tranSMART now supports arrayCGH and miRNA microarray data, different NGS data types, proteomics and metabolomics data. These different omics data types can each be analysed in the same tranSMART environment. Furthermore, the geneprint analysis has been added to allow integrated analysis of mRNA expression, proteomics and aCGH in a single visualization. One example is the work done within the Dutch CTMM Translational Research IT (TraIT) project, where tranSMART functions as the central data integration platform where exploratory analysis and hypothesis generation can be performed. Regarding molecular data, four domains are accommodated within TraIT: DNA and RNA next generation sequencing (NGS), DNA and RNA arrays, mass spectrometry proteomics, and various non-high throughput molecular profiling (NHTMP).

The TraIT project recently added the Cell Line Use Case (CLUC) dataset to tranSMART as a convenient dataset to standardize data formats and data processing pipelines from the four domains. It is also used to test the integration pipelines within the TraIT translational toolset. By incorporating the same platforms as used for ongoing research projects, this cell line set gives a representative test set comparable to real patient data, without the legal burden of handling personal data. Because of the unique, broad scope of this dataset and its potential use for biomedical data infrastructure the TraIT Cell Line Use Case dataset will soon be made available freely under an open data license.
Durrer Center for Cardiovascular Research

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Background
The Durrer Center for Cardiovascular Research (Durrer Center) is a non-profit national multi-disciplinary collaboration of academic research institutes in the field of cardiology, genetics and biostatistics partaking in cardiovascular genetic and epidemiological studies and associated biobanks. Durrer Center is an independent unit within the Interuniversity Cardiology Institute Netherlands (ICIN) located at the AMC in Amsterdam.

Durrer Center facilitates high-quality sample/data collection and storage for the Principal Investigator and facilitates maximizing its scientific potential by providing a transparent mechanism for sample and data access to benefit the scientific community and society as a whole.

Methods/approach
The Durrer Center provides autonomous and secure storage of both samples and data as well as tools for a) logistic support, b) research support on molecular biology and bio statistical analysis and c) trial management for the development of registries and standard e-CRFs for clinical data collection using OpenClinica.

Results
At the moment Durrer Center manages the samples and/or data of 35 (multi)center studies covering more than 250,000 samples and developed 11 e-CRFs. It is the preferred biobank for CVON (CardioVascular Research the Netherlands) and ICIN projects and collaborates with national and international partners such as CTMM (Center for Translational Molecular Medicine) and A*STAR (Singapore).

Lessons learned
The Durrer Center has gained an authoritative and leading role in the handling and organization of fractionated and scattered stored samples plus the accompanying data in the Netherlands. The Durrer Center combines existing cohorts and provides a web-based portal to exhibit available collections as well as guaranteed secure, independent and high quality storage of samples and/or data.
Standardized workflow for bio-material requests

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\textsuperscript{*}The work described in this study was carried out in the context of the Parelsnoer Institute (PSI). PSI is part of and funded by the Dutch Federation of University Medical Centers and has received initial funding from the Dutch Government (from 2007-2011).

Background/information:
The exchange of samples from biobank/lab to researcher or from hospital/lab to biobank is traditionally administered through e-mails, fax or telephone. This approach lacks a proper track-and-trace and audit trail of specimens, impeding a fast recovery of lost samples. In close collaboration with the Parelsnoer Institute (PSI)*, the TraIT (Translational Research IT) Workflow for requesting and distributing samples was developed. This workflow supports all process steps typically needed in a sample workflow: request of bio-materials from a specific biobank, evaluation and approval of a request, track and trace of the sample during shipment.

Methods:
The workflow tool has been developed in collaboration with CSC using the OpenText Business Process Modeling (BPM) platform in a use-case driven approach. The design has been based on the rules and recommendations outlined in the existing PSI biobanking protocols and SOPs. The various steps in the workflow are implemented as separate building blocks, and can be customized to the specific needs of any organization or multi-center collaborative network with biobank activities.

Pilot tests were performed in the PSI platform and the PCMM (Prostate Cancer Molecular Medicine) study. End-users from these two evaluated the workflow tool with simulated sample requests. Additionally the Workflow tool was assessed in parallel with the non-automated workflow procedures (telephone, mail, email) using a real-life DNA-sample request from the CVA(Stroke)-Pearl in the PSI platform.

Results:
The workflow was developed as a cloud based solution to monitor requesting, dispatching, collecting and processing bio-specimens from collections under full control of audit trails. Time constraints can be set and attachments can be added at every step in the workflow (eg. Material Transfer agreement, project proposal),
The tool is now hosted in a production environment (Vancis) and is actively used in TraIT projects as well as the PSI platform.

Conclusions:
A methodized cloud based workflow application for requesting, dispatching and collecting bio-materials from collections enables the users to work according to a standardized process, improving quality, reliability and accountability. Every process step is logged and location and/or status of the sample can be monitored at any point in the sample exchange process. Phone calls, fax and e-mails, used in the traditional sample logistics workflow, can be eliminated or at least greatly reduced.
BiobankConnect: a semi-automatic ‘ETL’ system for biobank data integration

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Recently biobanks have become one of the most important repositories for biomedical research and new biobanks are constantly emerging from all over the world. Although the amount of data has been increasing in individual biobanks, researchers still desire ‘bigger’ data to reveal subtle associations between phenotypes and diseases by combining data from multiple biobanks to deliver more statistical power. Unfortunately pooling data from biobanks is a huge challenge. An standardized ETL (Extract, Transform and Load) data integration process has been successfully used by the P3G project (Isabel Fortier, Public Population Project in Genomics and Society). In this process the biobank data are converted to a common standard (data schema) such that the data elements measured in individual biobanks are compatible or harmonized. However, this approach is still very time-consuming and requires both domain expertise and technical skills. There are two major challenges, I) finding the most relevant source data elements for target element, which is ‘like finding a needle in a haystack’ because the data elements are most of the time described differently, e.g. hypertension → high blood pressure; II) writing the data conversion scripts requiring technical background on the scripting language.

In order to speed up the data integration process, within BioSHaRE, BioMedBridges and BBMRI-NL we have developed a semi-automatic system (BiobankConnect) to assist researchers in pooling data from individual biobanks. First we use ontology based query expansion (e.g. hypertension → {increased blood pressure, high blood pressure}) in order to find relevant data elements from biobanks. Secondly, we automatically generate the data conversion scripts based on the data elements suggested by the semantic search, considering units that could be converted, categories that can be mapped automatically, and recurring conversion patterns (e.g. BMI). We have found that BiobankConnect can suggest correct mappings in over half of the cases and a good alternative within a top 10 of suggestions in 98% of the cases.

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MOLGENIS Workbench towards Personalized Genome Diagnostics

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High-throughput use cases such as multi-omics integration and NGS variant interpretation can now benefit from MOLGENIS adaptable upload formats and query performance, but also require a pre-filled toolbox to help process and understand these data. Therefore we also added extensible variant ‘annotators’ that enables easy data enrichment (CADD, FitCon, 1000G, ExAC, ClinVar, CGD, HPO, COSMIC etc.), application analysis protocols (risk prediction, monogenic diagnostic analysis, etc.) and supporting algorithms (discover de-novo variants, symptom-to-disease matching, genome build liftover, etc.). These annotators are also available as a command-line executable to enable use in routine analysis pipelines before uploading the results. Adding more annotators is currently done by implementing a minimal Java interface class. Visual inspection of genes and variants in a biological context is made possible by a WikiPathway-based viewer and Dalliance-powered genome browser.

In collaboration between BBMRI-NL, BioMedBridges WP8, UMCG and FIMM we have piloted a platform for Personalized Medicine data exploration geared to diagnostics. We build on MOLGENIS, a collaborative open source platform on a mission since 2002 to generate great software infrastructure for life science research. It has already produced a large variety of applications including patient registries, model organism databases, biobank catalogs and computational script generators. We have refreshed the MOLGENIS platform by moving from generation-time to run-time configuration, allowing the users to upload complete data structures, incorporating popular software tools like Maven, MySQL, SpringMVC, GitHub, Bootstrap, Java 8 and ElasticSearch. The resulting modular software suite generates rich web applications that feature an import wizard for flexible formats, APIs for REST and JSON, user and rights management, cross-dataset ontological harmonization, and of course data exploration tools including plotting, filtering, aggregation, complex queries, and metadata browsing. Many components have runtime extension points, meaning custom R plots and reporting templates in Freemarker can be defined and used to present data. Imported data is indexed using ElasticSearch to eliminate long loading times.

We expect the MOLGENIS community will continue to develop valuable Personalized Genomics Medicine exploration apps as well as function as a sharing platform for best practice data and pipelines, integration with international sharing platforms such as GA4GH and Cafe Variome (for which pilots are underway), well-curated reference knowledge-bases, and optimal user interfaces, results of which can disseminate into research institutes, clinical software companies and individual labs.

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The Netherlands Twin Register Axiom Biobank platform for GWAS

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No abstract available
AMC Biobank: A central biobank in an academic medical setting

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The Academic Medical Center is one of the foremost research institutions in the Netherlands, as well as one of its largest hospitals. Over 7,000 people work here to provide integrated patient care, teaching, and fundamental and clinical scientific research. Research is supported by core facilities including the AMC Biobank, which has been established in 2014. AMC Biobank provides comprehensive storage services for biological materials and related clinical data. The Biobank is part of AMC’s division G (Laboratory Specialisms) and works closely together with the Durrer Center for Cardiovascular Research, hosted by the ICIN–Netherlands Heart Institute. AMC Biobank and Durrer Center share people, rooms, protocols, and quality standards. AMC Biobank currently houses more than 750,000 samples for 29 (biobank) studies, including various Parelsnoer collections, shared with other Dutch university medical centers, the HELIUS study on health differences among the residents of Amsterdam with different ethnic origin, and the MARS study on molecular diagnosis and risk stratification of sepsis. A catalog, established in collaboration with CTMM-TraIT, provides metadata of all collections stored at AMC Biobank. By attracting more individual (biobank) studies, building a central site for storage of viable cells in liquid N₂, developing study-specific catalogs on sample level, and obtaining ISO9001 certification, AMC Biobank aims to become the central storage site for patient material dedicated to scientific research at the AMC.