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Considerations for a distributed, federated Expert Centre

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Considerations for a Federated Expert Centre

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Research Infrastructures of the Biomedical Sciences provide invaluable resources that serve academic and industrial research, education and innovation. However, their seamless and efficient interoperation on a European scale may incur considerable difficulties, which are among other reasons due to the fragmentation of the scientific community, legislation and ethical requirements.

Research and development related to prevention, diagnosis and therapy of human diseases requires the availability of high quality human biological samples and medical data. Biobanks are professional infrastructures for collection, preservation, storage and providing access to human samples and associated data. They can be established, for example, in the context of specific cohort studies (e.g., large population cohorts) or within the health service. Typically, donors or patients provide their samples and data to biobanks as donations, and biobanks are seen as a trusted, publicly funded environment that ensures the proper use of this precious resource for the benefit of certain patient groups or citizens, in general. This expectation can only be met if biobanked samples and their associated medical data are efficiently used in high quality research projects and their results lead to development of novel products (1-4).

The broad variety of methodologies that are presently available for the analysis of human biological samples exposes a particular difficulty: human biological material (tissue, blood and derivatives, and other body fluids) is an expendable, unique material which should be used in the most economical way possible. This has become increasingly important due to the growing understanding of the individuality of many diseases, such as cancer, where in most cases each sample may be regarded as unique, an understanding that led to the concept of personalized medicine. Moreover, due to improved diagnostics and screening programmes, tumours are detected at ever earlier stages, resulting in very small tumours that contain only little material, which often precludes multiple analyses. Similarly, blood samples are a limited

resource, in particular when they need to be collected from seriously ill patients. Here the problem of expendability is aggravated because different analysis techniques require different sampling technologies (e.g. stabilizers, anticoagulants or other preservatives).

While it is often highly desirable to apply several complementary methodologies of analysis to the same sample, the limitations described above often allow only one or two analyses. To harness the true potential of modern analysis technologies and the resources provided by the Biomedical Sciences Research Infrastructures, an approach must be found that optimizes the economical use of scarce material. The solution for this problem is not only the consistent use of optimized methodologies and analysis techniques that allow obtaining results from ever smaller quantities of human biological material. In addition, an integrated approach is required, comprising the conception and ethically and legally correct setup of the project, a unified pre-analytical workflow that can serve a broad spectrum of analysis techniques, finally converging to an integrated data analysis pipeline that combine the results of this multimodal analysis.

The Expert Centre concept

Already early in the preparatory phase of BBMRI-ERIC the need for a trusted intermediate for the use of human biological samples and data was recognized, between the academic and medical sectors on the one, and the industrial sector on the other hand (5). This need arose primarily due to the ethical and legal restrictions of using such samples in for-profit research: the Oviedo Convention on Human Rights and Biomedicine explicitly prohibits financial gain through using parts of the human body (6). This implies not only that samples must not be sold for whatever purpose, rather it creates a second problem: for-profit R&D would unfairly benefit from resources that were obtained through public funding (to the biobank, but also to the healthcare system in which context the samples are generated) creating a competitive advantage. Furthermore, since human biological samples are an expendable resource that cannot be fairly shared with everyone, their (exclusive) use by industrial research implicitly leads to competitive imbalance (7).

The solution was to introduce a trusted partner, an Expert Centre that converts samples into data that can then be shared unlimited, in principle. Their prioritized use by industry during a limited period can be subject to a fee that supports the operation of Expert Centre. After this grace period, the resulting high quality data must be made publicly available, following the FAIR principles (8). An Expert Centre itself is a not-for-profit part of the academic and medical sector and can thus reimburse the biobank for their efforts without incurring the risk of being stigmatized as profiting from the public good and thereby distorting equality of competition or buying human samples.

While this approach solved the problem for industry it highlighted the need to generate data from samples following best practices, standards and state-of-the-art methodologies, to allow data interoperability and reusability according to the FAIR principles.

Until now, BBMRI-ERIC has issued the third version of its document 'BBMRI-ERIC-Associated Expert Centres / Trusted Partners' that defines the basis for operation and acknowledging an Expert Centre. In brief, it must be a trusted partner who guarantees legal and ethical aspects of the donors' rights and intentions, who performs analyses of the samples in a highly standardized way according to the best methods available, resulting in high-quality data that a mandatorily returned to the public domain, becoming *F*indable, *A*ccessible, *I*nteroperable and *R*eusable.

Federated Expert Centres can provide an integrated multi-analysis pipeline

By definition, Expert Centres have several advantages over 'normal' laboratories regarding the mandatory use of state-of-the-art methodologies that follow European (CEN) and international (ISO) standards wherever possible, the explicit compliance with ethical and legal requirements and the commitment to serve the public good by depositing high-quality analysis data into public repositories, following the FAIR principles. However, the optimal use of human biological material is not automatically guaranteed by these operating principles.

To accommodate the need for optimized multimodal analysis of human biological samples the concept of Expert Centres needs to be expanded by integrating all required elements into a modular standardized workflow, thereby using samples as economically as possible (Fig. 1).
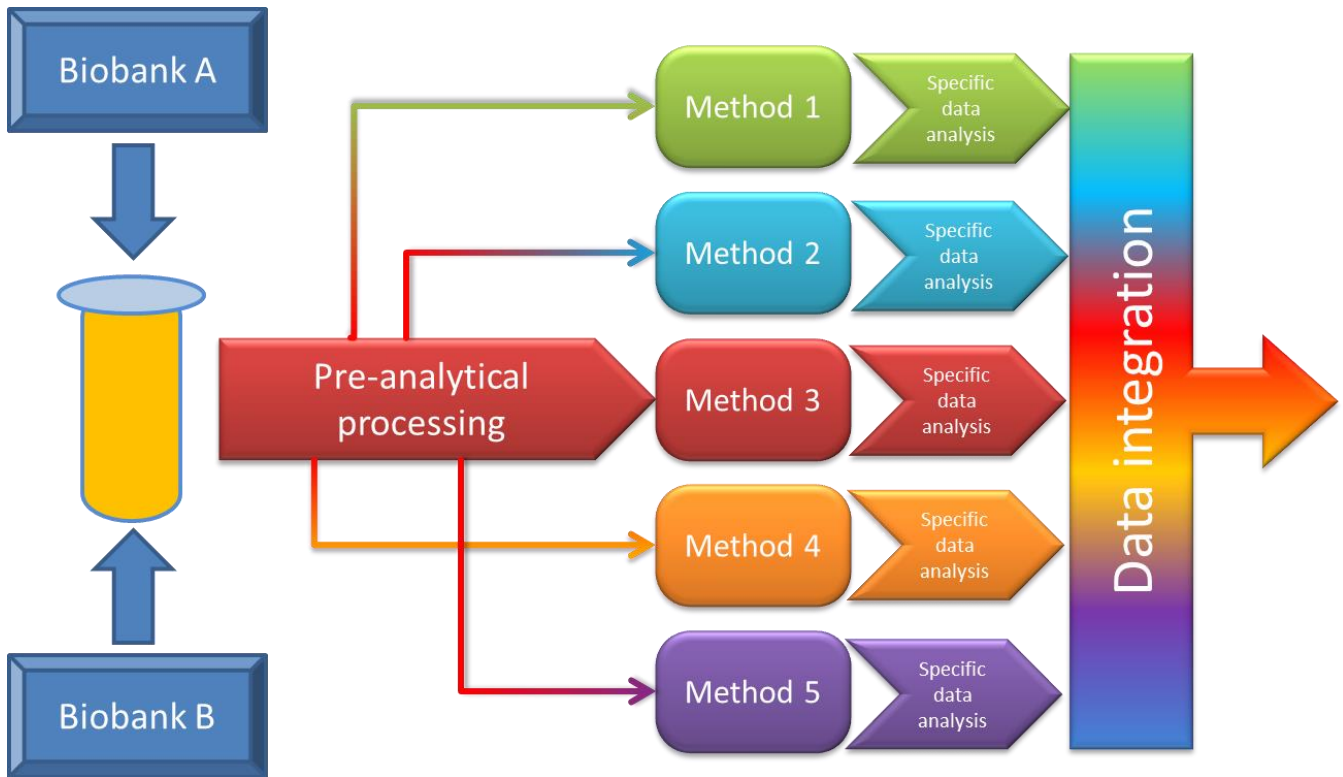

Fig. 1: Basic scheme of a federated Expert Centre. Samples obtained from (local) biobanks are processed along a common pre-analytical processing workflow that feeds into various methods. After method-specific data analysis joint data integration is performed.

This approach necessitates that the pre-analytical workflow must integrate all processes that are required for the delivery of analytes for the individual analytical methods. For several reasons it is highly desirable for biobanks to be centralized hubs with the expertise to provide high-quality material for analysis that was generated though standardized workflows: one is that the pre-analytical processing of most human biological samples must not be deferred and must therefore be performed by the biobank or an immediately associated laboratory. Another is that the association of biobanks as an integral part of Expert Centres supports the role of biobanks as providers for research and development and the optimal use of samples by a

broad range of analytical methodologies strengthens their position.

Therefore, integrated and standardized pre-analytical sample processing workflows that guarantee consistent high-quality results should be implemented locally or nationally and can then serve a transnational network of specialized analytical facilities and Research Infrastructures. Through such a structure, the most advanced methodologies that are otherwise not available locally/nationally can be combined while using valuable samples most economically though standardized, integrated workflows (red arrows) (Fig. 2).
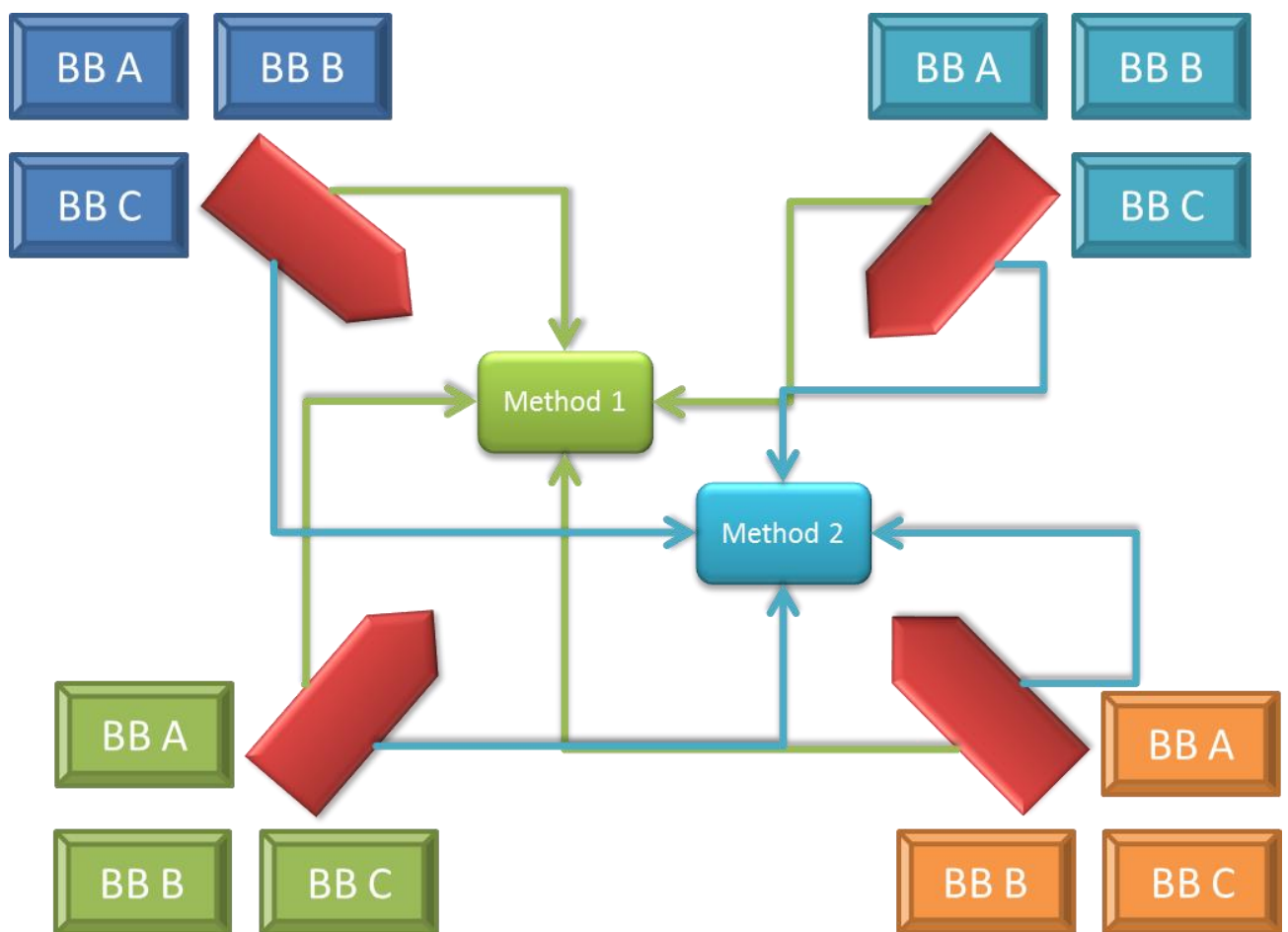

Fig. 2: Distributed federated Expert Centre: local/national biobanks (BB) individually or jointly implement standardized integrated pre-analytical workflows (red arrows) that provide analytical material to specialized methodologies that are not available locally or nationally.

Material for analysis is produced by the same standards by all the integrated pre-analytical workflows thus guaranteeing data of the same quality level that can be joined in the final data integration step.

Specific issues arising from the distributed nature of a federated Expert Centre

Advantages

A first advantage that is similar to the 'normal' Expert Centres is that analyses performed by any of its nodes will result in data that can be joined in analysis, since they will have been generated at the same level of standard and quality. This allows combining cohorts that previously could not be linked in a joint study. Falling short of adhering to the same standardized workflows does not merely imply compromised quality, the problem is rather that different procedures that all lead to good quality results that are, however different, because no 'true' result can be defined against which to validate these procedures. This was highlighted by a proficiency testing ring trial performed during the EU FP7 project BBMRI-LPC where it was clearly established that serum and plasma metabolome data were biased according to the biobank of origin, even though quality indicators were consistently indicating high quility (V. Ghini, et al., manuscript in preparation).

Another clear advantage of a federated Expert Centre, joining expert nodes with their own unique specializations, is that samples can be investigated not only by the most advanced methodologies, but that different types of analysis can be combined at the same high level of standardization, expertise and quality. This can lead to extended datasets that can be joined in analysis resulting in a much broader scope of knowledge, and a methodologically broad database ('multi-omics').

For the client of such an Expert Centre there is another specific advantage, because analyses will be guaranteed to be performed at the state-of-the-art and because a broad spectrum of different methodologies can be used transparently, i.e. without requiring the client to have

expert knowledge on which methods to apply and who to address for the m.

A networked Expert Centre has already been established in a simpler form: EXCEMET combines expert nodes that employ either of two complementary established methodologies for metabolome analyses, NMR and liquid chromatography/mass spectrometry.

Restrictions that need to be resolved

In several countries there are strict legal restrictions against exchange of human biological material and data. These may be alleviated in the future, e.g. in the sense that they might not include derivatives, which would allow a federated Expert Centre to work as described above, whereas the exchange of 'raw' human material could be still restricted. Moreover, a networked, federated Expert Centre, consisting of nodes that represent the leading institutions in their field in Europe is in a good position to attain intergovernmental status, similar e.g. to the EMBL, or, to become part of such an organization.

It is evident that a Europe-wide legal mechanism regulating unhindered sample and data exchange is urgently needed to reap the benefits of the specialized resources which are not available in each and every member state. Such a distribution mechanism must also extend to joining different Research Infrastructures for which an operational concept has been already presented as M46 of the H2020 project CORBEL.

Summary: A federated Expert Centre requires standardized pre-analytical workflows

The conversion of human biological samples to high-quality datasets is an involved process chain that requires integration of all steps along this workflow. Each step will need to define prerequisites for processes upstream (in the sense of quality and documentation of fitness-for-purpose) and need to validate its output for the downstream processes (documentation of fitness-for-purpose). While this is relatively straightforward for single-purpose workflows it can become quite involved for those steps in a multi-purpose workflow that feed several methodologies. The pre-analytical centre that produces input for several advanced

methodologies must thus validate its output for all of them (e.g. production from a single sample of high-molecular weight DNA and RNA for sequencing and of frozen histological sections for in-situ technologies). While this is certainly challenging for this node (e.g. a pathology institute) it is feasible, matches the interest of biobanks and is much more economical in terms of cost, implementation of standardized methodology and sample consumption than sending out tissue pieces individually for specialized pre-analytics and analytics.

References:

1.   Asslaber M, Zatloukal K. Biobanks: transnational, European and global networks. Brief Funct Genomic Proteomic 2007;6:193-201.
2.   Hewitt RE. Biobanking: the foundation of personalized medicine. Curr Opin Oncol 2011;23:112-119.
3.   Riegman PH, Morente MM, Betsou F, de Blasio P, Geary P, Marble Arch International Working Group on Biobanking for Biomedical R. Biobanking for better healthcare. Mol Oncol 2008;2:213-222.
4.   Simell BA, Tornwall OM, Hamalainen I, Wichmann HE, Anton G, Brennan P, Bouvard L, et al. Transnational access to large prospective cohorts in Europe: Current trends and unmet needs. N Biotechnol 2019;49:98-103.
5.   van Ommen GJ, Tornwall O, Brechot C, Dagher G, Galli J, Hveem K, Landegren U, et al. BBMRI-ERIC as a resource for pharmaceutical and life science industries: the development of biobank-based Expert Centres. Eur J Hum Genet 2015;23:893-900.
6.   Council of E. Convention for Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Biomedicine: Convention of Human Rights and Biomedicine. Kennedy Inst Ethics J 1997;7:277-290.
7.   Mascalzoni D, Dove ES, Rubinstein Y, Dawkins HJ, Kole A, McCormack P, Woods S, et al. International Charter of principles for sharing bio-specimens and data. Eur J Hum Genet 2015;23:721-728.
8.   Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, Blomberg N, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016;3:160018.