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19 February 2019

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Report by the external peer review committee

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Gareth Bicknell
Geert van der Veen, Anke Nooijen (rapporteurs)

Executive summary

This report presents the results of the peer review of the Integrated Biobank of Luxembourg (IBBL) of the Luxemburg Institute of Health (LIH). The review covers the period 2014-2017 and considers research strategy and quality, scientific and societal impact, and the management and governance.

The audit was performed by an independent external assessment committee, consisting of two internationally renowned experts in the field of biobanking, Dr. Gabriele Anton (chair) and Dr. Gareth Bicknell. Geert van der Veen and Anke Nooijen (Technopolis Group, The Netherlands) acted as support for the peer review committee.

The committee would like to thank everyone involved in preparing and implementing the hearing at the LIH-IBBL, for making the documentation available, and for participating in interviews.

The committee concludes that the IBBL is serving its base of clients and the majority of its stakeholders to standards equivalent to very good international practice. The IBBL is a strong player in the international biobanking field (both at the processing and storage level), and among the best in the world with regard to its engagement in biospecimen quality and method standardization. It is managed well, demonstrating appropriate independence and a research focus, public outreach of international standard, and it has extremely competent and motivated staff. The infrastructure and working conditions are outstanding, being well above average on the international scale.

The six services that the IBBL offers all run very successfully, as can be seen by increasing number of projects overall, as well as the number of projects per customer, and the uptake of services not traditionally associated with biobanks. As a result, the IBBL foresees that it may eventually be necessary to reject work, if further expansion is not possible. A decision should therefore be taken about which direction is more important to the IBBL's future (expansion or focus of research).

The key points to improve addressed in the report relate to the IBBL's integration with the Luxembourg (LU) research landscape. The committee feels that LU research could benefit to a much higher extent from the services that the IBBL offers, as well as from their international visibility, and so a higher priority should be given towards the support of LU biomedical research, especially in regard to the IBBL's significant Government funding. The following recommendations were made related to this:

- Revisit the strategic model to elevate the importance of support to the Luxembourgish research community over the international partnerships
- Improve communication on strategies, project prioritization and sample access policies towards Luxembourgish researchers
- Improve communication on block grant spending towards stakeholders
- Increasing IBBL's international visibility should be seen and communicated as a tool to help LU research grow, and not as a mission in itself.
- Create a new KPI to monitor IBBL's value to smaller-scale national research
- Develop a simple and openly available pricing system for sample access, sample storage and services, that benefits LU over external customers

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1 Introduction

1.1 Background

This report presents the results of the peer review of the Integrated Biobank of Luxembourg (IBBL) of the Luxemburg Institute of Health (LIH). LIH has the mission to deliver scientific, economic and societal value for Luxembourg by performing research, studies and developments in the fields of clinically-oriented biomedical research and public health. LIH's activities lead to the generation of new knowledge in disease mechanisms, epidemiology, diagnostics and treatments of human diseases, and they improve the understanding of health determinants and of the financial structures of health care. Since its launch in 2010 the IBBL has positioned itself as an international centre of excellence in biobanking.

The peer review is part of an evaluation of the three public research institutes under the responsibility of the Luxemburg Ministry of Education, Science and Research (MESR). The evaluations cover the period 2014-2017 and take into account scientific performance, relevance for society including client and partner interaction and the governance and organisation as requirement to sustain the ability and suitability for promoting both scientific performance and interaction with clients. The evaluation has been assigned to Technopolis Group (www.technopolis-group.com).

The results of this peer review feed into the evaluation of LIH as an institute and into the evaluation of the three institutes at national level. For this reason, the chair of the IBBL peer review also participates in the peer review of LIH at institutional level. The results are intended for MESR to (re)define their relation to the institutes; for the institutes to help them to improve their performance further and for other (mainly public) stakeholders to use as they find suitable.

The peer review set-up has been designed by Technopolis Group, based on the Terms of Reference from MESR. It aligns with good practices used in many evaluations.

1.2 Composition of the Committee, independence, data provided and procedures followed

1.2.1 Composition of the Committee

The audit was performed by an independent external assessment committee, consisting of two internationally renowned experts in the field of biobanking:

- Gabriele Anton, HMGU biobank (chair). The HMGU Biobank is a core facility of the Helmholtz Center Munich, a publicly funded research center. The biobank offers services to Helmholtz researchers and external collaboration partners and contributes biobanking infrastructure and service in a number of third party funded projects. The main focus of the biobank is on liquid biosamples from large epidemiological studies.
- Gareth Bicknell, Human Biomaterials Resource Centre (HBRC), University of Birmingham. The HBRC is an academic biobank with close ties to multiple hospitals in the UK. Its core services include fluid/solid sample processing and storage, a complete histological pathway from fresh tissue to digitised immunochemistry, and the enablement of research via its own generic ethical approval. The HBRC is entirely self-funded through charges to non-commercial (grant funded) and commercial clients.

Short CV's from all assessment committee members are attached in Appendix A.

Geert van der Veen and Anke Nooijen (Technopolis Group The Netherlands) acted as support for the peer review committee.

1.2.2 Independence

Any existing personal or professional relationships between committee members and programmes under review were reported and discussed in the committee meeting to safeguard an independent assessment of the quality of LIH-DoPH and its research programmes in an unbiased and independent

way. The Committee concluded that there were no close relations or dependencies and that there was no risk in terms of bias or undue influence.

1.2.3 Data provided to the Committee

In preparation of the review the peers received the following information:

- A self-assessment report (SAR) of LIH at institute level
- A self-assessment report of the IBBL
- A background report for the peer review of LIH prepared by Technopolis Group, including a.o. an analysis of the participation of the IBBL in FNR and EC research projects and a bibliometric analysis of the publications of the IBBL (by ECOOM).

The assessment in combination with the discussions of the peer review committee with the research leaders, researchers and stakeholders allowed an objective evaluation of the IBBL.

1.2.4 Procedures followed by the Committee

The final assessments are based on the documentation provided by the Institute and the site visit to the IBBL in Luxembourg on 12-13 September 2018 (programme in Appendix B)

At the beginning of the site visit, the Committee was briefed by Robert Kerger of MESR and Geert van der Veen and Anke Nooijen of Technopolis Group about the objectives of the evaluation in general and of the evaluation by the committee in particular. During this meeting, several questions were clarified. The Committee also agreed upon procedural matters and aspects of the assessment.

At the end of the site visit and interviews the Committee discussed the conclusions and recommendations. Preliminary draft conclusions were presented to the participants in the discussions including the management of the IBBL and LIH and representatives of the Ministry of Higher Education and Research (MESR) and the Ministry of Health.

A first version of this report was drafted by the peers in the week after the site visit to Luxemburg. The report was finalised through email exchanges. The consolidated version was presented to the Institute in October 2018. The reaction of IBBL was discussed between Technopolis and IBBL. The comments were submitted to the Committee and led to some adjustments of some factual points. The final report was then submitted to MESR.

For the assessment of the quality of the research, the IBBL was compared at the international level with its peers. Publication and citation records were examined; major achievements were considered and the capacity to be competitive in application to international funding and in attracting highly qualified students and collaborators was discussed. The relevance of the IBBL in relation to health research was judged at the international and national level. Services and expertise rendered to private and public clients and partners and the impact on the general public served to assess the relevance for society.

The aspects of governance and organisation of the IBBL were mainly focused on the discussion about the strategy with IBBL staff members. The findings are presented in this report. The findings related to the organisation show adequate robustness, since they have been discussed with the most relevant stakeholders. The findings related to the positioning of the IBBL within LIH and the positioning of LIH in the health (research and education) landscape in Luxembourg and in international perspective give the reflection of the peers on the vision of the IBBL but require further input from other stakeholders inside and outside LIH. Therefore, these findings are preliminary and will feed into the evaluation of LIH at institute level.

2 The positioning of the IBBL research: rationale and strategy

2.1 IBBL strategy and targets

According to the self-assessment report (SAR) prepared by the IBBL, its mission is to provide accredited biospecimen-related services and a biobanking infrastructure for applied medical research. This is indeed a normal mission of a biobank and is perfectly fine.

The IBBL's vision is to be an international centre of excellence in biobanking and a valued partner in developing better healthcare solutions. Given that a very high proportion of the IBBL's funds come from the Government contribution or block grant, we recommend revisiting this. The vision should, in our opinion, reflect the funding and give a high(er) priority towards support of the Luxembourg (LU) biomedical research.

It should be noted though, that MESR in the performance contract 2014-2017 specifically asked IBBL to develop this external visibility, by getting Horizon 2020 funding and signing contracts with third parties.

The IBBL's strategic goals have been adjusted in the 2018-2021 performance contract to serve two main audiences, i) support Luxembourg biomedical research; ii) be a preferred European partner for accredited biospecimen-related services and biobanking infrastructure. These goals are acceptable regarding content, but they should be rearranged to reflect the clear priority of supporting LU research. International cooperation and visibility is of course important for the IBBL, but it should be seen more as a tool to help LU research grow. It is important that this is also recognised by MESR.

Overall, both goals are addressed very well by the IBBL, but a clear prioritization towards LU research is missing. According to IBBL efforts have taken place to reach out to the LU research community, such as the launch of a new call system of the Personalised Medicine Consortium (PMC) that was initiated and co-funded by IBBL and the communication about IBBL's service at each PMC annual meeting and LIH "city hall meetings. However, the Committee's impression is that, at present, more effort is made within international projects and towards international visibility, which is also reflected in outside communications (website, business cards). One reason for this seems to be a lack of requests by LU researchers, but then more efforts should be undertaken by the IBBL to tailor services to the needs of LU researchers and to make LU researchers aware of the opportunities the IBBL presents to them in a systematic way. In this context, the education of researchers in sustainable use of biomaterial, and in the importance of the pre-analytical quality of biosamples, becomes an important mission of a biobank. FNR could support this by emphasizing these points in their calls and thereby promoting the use of the IBBL by LU researchers.

It seems also that there are certain services provided by the IBBL which are not systematically taken up by researchers within the LU research community. This is to some extent the fate of all biobanks, but efforts should be undertaken to overcome this by actively informing the LU research community on IBBL's strategies, investment of block grant, and pricing system. A pricing system that clearly benefits LU research by increasing costs to external customers while lowering those for LU could also help in this context.

The overall number of projects conducted by the IBBL is constantly rising, which is of course an indicator of the high quality delivered by the IBBL and the satisfaction of its customers. But due to the high work load foreseen in many areas (EORTC, PT, INSERM cohort) the IBBL will probably have to refuse projects in the future. Therefore a decision should be taken which direction to take in the future (expansion vs. focus on certain areas). Additionally a process for approval of projects should be put in place and the criteria and process of decision taking should be communicated within LU.

The thematic scope of the IBBL is very well suited to a biobank and is due to the broad biospecimen research programme, the innovative biomarker validation programme, and the unique proficiency testing programme broader than that of most biobanks. Eventually the IBBL will need to focus on fewer activities, if expansion (mainly within personnel) is not possible.

With the biobanking services it provides, and with its efforts within biospecimen science, the IBBL is a well suited partner for biomedical research and acts as "research enabler". LU researchers should clearly be encouraged to use the possibilities it offers.

2.2 IBBL clients and stakeholders

The demands on the IBBL are clear, and there is no question that the IBBL delivers high quality, reliable biobanking in a centralised location. The IBBL adds value to investment by additionally providing processing services, kits to improve sample collection, biobank training and proficiency testing, biospecimen research, and there is frequent engagement with both traditional and social media.

The SAR provided by the IBBL begins with a clear statement (attributed to B. Clément) that indicates who the clients and majority stakeholders should be – academic *and* industrial researchers. It notes that the IBBL's most important partners are its sister departments in LIH, the Luxembourg Center for System Biomedicine (LCSB) and the Life Science Research Unit (LSRU) within the University of Luxembourg, the Luxembourg hospitals, and the Laboratoire National de la Santé (LNS). It states that the main projects being supported are the Plan Cancer Collection (PCC), the NCER programme on Parkinson's, the Personalised Medicine Consortium (PMC) collaborations, and Principal Investigator (PI)-driven collections. It lists international partners as including EU-funded consortia, other public/private consortia such as European Organisation for Research and Treatment of Cancer (EORTC) and Breast International Group (BIG), INSERM, and industrial partners such as Precision Bioservices, Bayer, Novo Nordisk, and Qiagen.

In the wider context of the term "stakeholder", the Luxembourg government is a particularly important stakeholder. The IBBL also demonstrates, through its main website's *News* and *Get Involved* sections – as well as its traditional and social media interactions – that it does not forget the patients and healthy donors who place their trust in the IBBL. Other important stakeholders are the laboratories which participate in the proficiency-testing scheme. In the widest definition of "stakeholder", of course, the staff and management of the IBBL itself should also be included – the performance of each team member affects the prospects of the whole IBBL.

When it comes to how well the IBBL serves its stakeholders, the review detected a lack of information for certain key stakeholders (such as MESR, LIH, LCSB, CHL, LNS…) about the level of the IBBL's support (financial and scientific) to LU-based research. Furthermore, while it was clear that major national initiatives are being supported (PCC, NCER Parkinson's), as with many biobanks, a lack of information about small-scale support may be leading to an erroneous perception that support is only for the large consortia, or that biobanks are no more than commercial entities. We were presented with some evidence that a large number of Luxembourg initiatives were supported, but this should be communicated more widely to their stakeholder community.

Notwithstanding, once projects have been given a go-ahead, in 93% of 125 cases they have been managed by Project Managers using PRINCE2 methodology. This is excellent practice that is rewarded by excellent client feedback. The IBBL conducts an annual client satisfaction survey, from which it claims a 90% satisfaction score from a significant population of respondents. During interviews with the peer review committee, two LU projects and two external projects reiterated a high level of satisfaction with the IBBL, struggling to think of improvements to the service provided. Such feedback is rarely observed in biobanking circles.

Even so, the IBBL has suffered from setbacks – under-collection of samples due to funding rules, and a lack of space recently rectified by whole-scale move to a new premises – but in other respects, the IBBL is actually a victim of its own success. During discussion, it was stated that not all projects can be supported (a problem encountered by many of the most productive biobanks). The IBBL's own SWOT analysis indicates a reliance on a few large customers. This reliance may not be something that can be remedied easily, but better communication of the support for small-scale projects might clarify the way in which national funding is used for a wide range of Luxembourg projects. Indeed, the IBBL 2018-2021 Strategic Plan (part of IBBL's self-assessment report) itself states that increased transparency and preferred pricing, and better communication to LU researchers is a priority.

It was very clear during discussion that staff are highly satisfied, on a professional and personal level, with their working conditions, and with management support. This is a critical group of stakeholders often overlooked, but it is an important one, since – when quality is secondary only to traceability – a biobank can only benefit from having such content, well-motivated staff (especially when they are as skilled as those in the IBBL).

The IBBL's dedicated website looks professional, and it provides an overview to the public and researchers about what the IBBL does. There are links to social media. The presentation of projects helped in a variety of formats (small-scale/large-scale projects supported by year, links to public-domain lay summaries) would further engage both public and researchers alike.

In addition to the main website, the IBBL is unique in offering other useful resources to its current and potential stakeholders, including an online QC assay selector, an ISBER-approved pre-analytical self-assessment tool, and a sample annotation coding algorithm.

In conclusion, the IBBL is serving very well its base of clients, and its wider stakeholders – however, there are areas of communication and information which could be improved to facilitate enhanced visibility and use nationally.

3 Assessment of LIH-IBBL

3.1 Research quality

As stated in the SAR, the IBBL itself is not primarily a research organization – as a research infrastructure, it is rather an enabler of research performed by others. For this reason, the default research evaluation questions developed for the Luxemburg Institute evaluations are not considered appropriate, and this audit has focused instead on the six areas of operation highlighted below.

The fact that the IBBL does not (apart from its biospecimen research) pursue its own research agenda is important to maintain the neutral nature of the IBBL as service provider towards a variety of customers from different research institutes as well as from industry.

Notwithstanding, the IBBL does perform limited research on biospecimen quality, and not only does this render the IBBL unusual (even unique) amongst biobanks, but it has the potential to improve *all* research involving human material, nationally and internationally ("better science through better samples"). It is beyond the scope of this particular audit to advise on national research funding priorities, but it could be argued that a national policy of allocating a small amount of annual research expenditure to biospecimen research would ultimately lead to higher-quality, more efficient research expenditure in the traditional areas of funding.

The IBBL has structured its operations into six bioservices it offers to the scientific community.

3.1.1 Biobanking

The first service, biobanking, comprises the key processes in every biobank: to receive, adequately store long-term and retrieve upon request biomaterials of different nature (liquid, tissue) including associated data. At the IBBL all steps are conducted according to standard operating procedures (SOPs) within a dedicated quality management system and rely on a strong IT component (all steps mapped in laboratory information management system (LIMS) system). The service includes the provision of consumable kits for sample retrieval and in some projects the sample retrieval as such.

According to two customers interviewed (PI from the University of Luxembourg, BIG), the customer survey conducted in 2016 and 2017 (presentation Catherine Larue) and as seen by the increasing number of projects per customer, this service is performed very well at the IBBL. Equipment and processes are suited and the project management is highly professional and well structured (dedicated project manager for every customer). It was especially pointed out by customers that the IBBL staff members are very helpful and act proactively to tackle occurring challenges. Regarding the customer survey, a striking response is that 90% of customers would use the IBBL's service again but only 53% would recommend it to colleagues. It would be interesting to establish why satisfaction would not lead to recommendation.

At present, 37% of samples are collected and stored in the context of services (presentation Catherine Larue). At the same time only 26% of projects are conducted within research collaborations (SAR). We recommend intensifying the collaboration with LU researchers with the aim to apply for common research grants where the IBBL provides biobanking services as a partner in the grant. To this end, the needs in the LU research community should be assessed and services tailored to them.

An important service highly benefitting LU research would be a generic tissue collection, as has been foreseen in the Plan Cancer Collection. Implementation, however, has yet to be initiated. Obstacles preventing this should be identified and removed by all partners involved to enable a start as soon as possible.

Regarding the use of samples from open collections, the access policy to samples, as well as the prioritization of sample requests, should be openly available to reinforce the fact that sample access is subject to rigourous review. On its website, the IBBL presents a well-designed "eCatalogue", which could foster such thoughts (sample catalogue like an Amazon catalogue) – it is important to state the access policy within the same context on the website. Currently IBBL's sample access procedure and policy

cannot easily be found online. IBBL has a website for patients and healthy individuals (https://www.biobank.lu).

Ultimately, it is also important that the cost recovery for requests of open access samples should be implemented in a way that charges researchers from abroad higher, and therefore benefits LU researchers.

3.1.2 Sample Processing

The second service offered by the IBBL comprises a comprehensive sample processing service, whereby raw samples can be derivatised to common or custom products. For example, blood can be processed to plasma, serum, buffy coat, PBMCs, nucleic acids; or tissue to cryoblocks/cryocores/cryosections, FFPE blocks/sections, cell cultures, or to nucleic acids/mononucleosomes/proteins; or stool samples to microbiomes; or urine to cells, cell-free products, or DNA.

Processing is performed according to SOPs to ISO 9001 (the IBBL is one of the few biobanks to attempt this), harmonised with pre-analytics, post-processing QC, and SPREC annotation. Processing is automated when possible using multiple robots (liquids, cell selection, TMAs), and manual when not (centrifugation, sectioning), but the automated processing lacks the seamless integration with the LIMS that is desired, with the result that a large quantity of paperwork is necessarily produced when otherwise data could be captured electronically at source. Tracking of samples and products is via 2D barcoding, and there is sufficient critical redundancy in the liquid handling equipment to meet the current needs for robustness under pressure. Care will be needed to maintain this robustness through adequate further provision of equipment as the workload increases.

The quality of processing is considerably enhanced by the provision of sample collection kits to the collection sites. This represents a significant amount of work on the part of the IBBL staff, particularly for the large-scale collaborations. It not only improves research quality in a theoretical sense, but it saves money/improves productivity in the form of reduced QMS-mandated follow-up, reduced repeat sampling, reduced loss of precious sample resources, and reduced failure of studies due to insufficient quality. The societal impact speaks for itself – better science brings more rapid progress and innovation that is more robust. Finally, IBBL's contributions to international collaborative projects reflects well on the quality of Luxembourg research in general.

An enumeration of samples processed through automation vs total practical throughput was not provided (or indeed, requested), so it is recommended that this be a suitable metric to aid future planning.

On discussion of services with internal and external clients, it was clear that they were highly satisfied with the provision to date.

3.1.3 Sample analysis & quality control

The IBBL offers a range of quality control and quantification assays as well as some analysis techniques for annotation of samples (e.g. 16s rRNA sequencing) plus in house development service. We consider it outstanding that all these assays are validated and under strict quality management. The service the IBBL offers within this section is in its completeness and quality excellent and unique in the biobanking sector in Europe, maybe worldwide. It constitutes an important service for researchers.

It seems, however, that these services are mainly used by external customers. The use by LU researchers should be fostered, maybe through services tailored to LU needs and incentives for first LU users.

The biospecimen research conducted at the IBBL is, in its quantity, unique in Europe. We consider it important not only for the LU but also for the European biobanking community that this effort is continued and funds are made available for this. The IBBL applies a good combination of research activities to stay at the forefront of innovation (e.g. in the liquid biopsy sector) and a subsequent offer for a service that can bring revenues. The IBBL could consider recovering part of the costs for the research by charging more for the services. The collaboration with LU research on this topic should be

intensified, e.g. through common PhD thesis that have a biospecimen research part. This could also bring about common applications to research grants together with LU researchers.

Not all laboratory equipment seems to be heavily used at all times by the IBBL. It could be offered to collaborating scientists; however, this seems not to take place much. Therefore we encourage the IBBL to offer the equipment more proactively (providing this does not interfere with quality assurance, of course). This would also foster the interaction of the staff with other LU research departments, which at the moment seems not to be very intense. Additionally other formats could be found to increase scientific exchange for the IBBL staff (e.g. journal club, workshops with other LIH departments or LU research institutes).

The biospecimen research topic is an important basis of all other research, a fact that is unfortunately not yet recognized sufficiently widely in scientific research. Biobanks have an important educational role here. Therefore we recommend that the IBBL intensifies the communication efforts on this topic, maybe by hiring a person dedicated to this. The IBBL could also consider to offer consultation in quality management, especially under the new ISO 20387 norm, in quality control assays and method validation.

3.1.4 Biomarker validation

The essence of "validation" is the provision of objective evidence that a claim made is true in real-life practice. The use of validated biomarkers and methods are already fundamental to diagnostic laboratories, and their use in research is today considered increasingly relevant. The biomarker validation (BMV) service is a relatively new one for the IBBL, comprising Pre-Analytical, Analytical, Clinical Verification, Method Comparison, and QC Material activities, summarised into a final report for the client.

Since it is a service, rather than research *per se*, the value to society is very much down to the client, rather than the IBBL. That being said, the quality of the validation is paramount. Validation work is compliant with ISO 17025, against which the IBBL has been accredited by OLAS, so the quality of work is *de facto* high.

Despite the newness of the service, the IBBL was able to cite three examples of biomarker validation: (i) contract research for a biomarker in latent tuberculosis, funded by INSERM, as the first of four biomarkers to be validated, (ii) collaborative work with the University of Luxembourg for MYO5B funded by the FNR, and (iii) an INTERREG NWE grant for performing four biomarker validations. It has plans to continue service expansion.

Although not technically included in the term "biomarker", the IBBL also offers a validation service for instruments and kits. In most instances, this work is paid-for by well-known commercial companies, including Genotek, Qiagen, FluidX, Tecan, Becton Dickinson, and Clearbridge. The rationale is that in performing this work, the IBBL maintains its knowledge and skill-base in technologies at the fore-front of biospecimen research. When not paid, the IBBL aims to secure collaborative publication. For example, the IBBL was the first organization to validate CryoXtract, and the first to validate a rapid automated technique for PMBC isolation.

While there are plenty of testing laboratories accredited to ISO 17025, the IBBL is highly unusual – perhaps unique – in being both the accredited testing laboratory *and* a source of the material needed for the validations. This is an interesting approach that should be continued, since it represents a useful source of income not normally available to biobanks.

As a service, the costs are not insignificant, but they are essential when translating an interesting piece of basic research into a diagnostic tool for clinical work. The close ties between IBBL and LU research could be exploited to give a financial advantage to commercialisation of LU-originated discoveries over those originating elsewhere.

3.1.5 Biospecimen proficiency testing

The IBBL provides annual proficiency testing (PT = ring trials) to biobanks and laboratories. Currently, 21 processing and testing schemes are offered. The IBBL is the only biobank worldwide that offers such testing adapted to biobanking needs. The programme is endorsed by ISBER (International Society for Biological and Environmental Repositories).

The PT programme constitutes a big effort for the IBBL, and it is an important building block of high sample, and therefore research, quality worldwide. The programme has grown over the years as has the number of customers. It is by now self-sustaining and could bring revenues in the next years. The IBBL should consider allocating more resources (personnel) to it, as the work load is high and efficient and timely management is a precondition for the future success of the programme.

It seems however that it is mainly used by customers from outside LU. Therefore (financial) incentives for LU researchers should be considered. FNR could also encourage the use by asking for quality control measures for biospecimen used in grant funded studies.

Overall, the PT and BMV programmes are important contributions to a higher quality and reproducibility of studies involving biomaterial worldwide. If work load becomes too high for the IBBL, some kind of collaboration/franchising of these programmes to further biobanks could be considered.

3.1.6 University biobanking certificate

In addition to its participation at international conferences on research and biobanking, and its publications in peer-reviewed journals and book chapters, the IBBL offers a 3-week course in biobanking, co-organised with the University of Luxembourg and endorsed by ISBER. Participants attend from Africa, Asia, and Europe, and there is a reported 92% satisfaction, with a significant class size already booked for 2019.

Timing constraints did not permit further exploration of this activity, though it should be noted that the IBBL is one of a select few organisations offering a formal certificate which does not rely purely on self-teaching (the others being Biobank Graz [Austria], University of Minnesota [USA], Catholic University of Lyon/University of Nice-Sophia-Antipolis [France], Karolinska Institute [Sweden], PRIM&R [USA], and University of Groningen [Netherlands]).

The societal impact in terms of research productivity and quality, enhanced skill-base and likelihood of researchers winning grant funding, can only be improved by increasing the number of LU researchers attending this course. Attendance should be encouraged, and as uptake increases, sufficient resources will need to be allocated, perhaps funded through the usual educational funding streams.

3.2 Innovation quality and impacts

As a research infrastructure the IBBL acts as a service provider to research and therefore as a research enabler. With its focus on biospecimen quality and on adopting standards for biobanking, the IBBL has proved itself a leader in the biobanking field and has broad international impact in this respect. By its commitment to high biospecimen quality it increases the value of its clients' research, and it raises the profile of reproducibility in research, which of course forms the indispensable basis of successful science. The efforts of IBBL staff members Fay Betsou and Sabine Lehmann in the working group for the ISO 20387 norm need to be specially acknowledged in this context.

The IBBL constantly works towards standardisation of methods for new biospecimen types (e.g. stool, PBMCs) and new analysis techniques (e.g. liquid biopsy). This serves as basis for the wider application of these biospecimen or analysis techniques in biomedical research and clinical implementation and is therefore an important contribution to innovation.

The BMV service is a new and innovative tool that the IBBL offers to researchers to gather data on reliability and standardization possibilities for potential biomarkers. It will allow a better assessment of the clinical utility of such potential biomarkers and thereby can close the gap between basic biomedical research and clinical testing of biomarkers.

The IBBL has many international collaborations as well as international customers and is involved in European and international consortia (JPND, JDRF, H2020, EATRIS, IMI, ISBER). These international connections are already used to a certain extent to promote LU research but this could possibly be intensified. Within common EU proposals, LU institutes could profit from the international experience and visibility of the IBBL as modern research infrastructure.

3.3 Management and governance

The IBBL exhibits a mixture of integration with, and independence from, the LIH, to the extent that it possesses its own CEO, Catherine Larue, who reports to the Board of Directors, just as the LIH itself has a CEO who reports to the Board of Directors. Whilst undoubtedly an unexpected arrangement, it does have its merits. The IBBL shares core administration with the LIH – IT, HR, purchasing, contract tracking, general finance – but it also retains a certain degree of independence. This is highly desirable in a facility for which the mission is to raise the profile of *all* LU medical research (not just the LIH's), as well as making Luxembourg itself a preferred focus for international collaboration. It is essential in the context of international collaborative projects with research partners, where IBBL benefits from being seen as clearly neutral.

The Board of Directors (BoD) meets 4-5 times a year, and it consists of at least one non-voting Ministry Commissioner, plus 9 members with competence in research, research management, or economic impact. Scientific strategy is decided on advisement by the Scientific Advisory Board, comprising 3 non-LU scientists), that meets at least yearly (according to the SAR).

For more routine matters, the IBBL's Executive Committee meets at least every second week, and it is composed of the CEO, LIH's Chief Financial and Administrative Officer (CFAO), data Protection Officer (DPO), IBBL's Quality Management (QM) and Marketing and Communication (MarCom) managers and IBBL's thematic groups leaders. The committee is responsible, amongst other things, for reviewing finance, taking no/no-go decisions on projects, assessing KPI performance, and making recommendations to the BoD – matters which would not be expected to be freely advertised to all.

The Sample Review Committee (SRC) considers access requests (both LU and foreign), and it consists of two IBBL staff, the PI of the sample collection, a patient representative and a clinician. In biobanking circles, there is some debate whether – and in how much detail – the results of consideration should be published. On the one hand, no-one wishes to publicise rejected requests. It can also be considered unwise to trumpet approval of projects for which the success is unknown. On the other hand, publication of lay summaries (that do not betray too much intellectual property/strategy) not only serves the public interest, but it demonstrates the breadth and frequency of requests being made of a biobank.

During interview, reference was made to a "grid" to determine no/no-go decisions on projects – this should assist in fair, open and proportionate decisions. However, it was evident that the use of this grid, and at least an indication of the decisions resulting from it, does not seem to reach all stakeholders with a valid interest in knowing. This results in a lack of awareness on the side of key stakeholders (such as MESR, LIH, LCSB, CHL, LNS…) about the level of support (financial and scientific) being given to LU-based research.

Furthermore, while it is clear that major national initiatives are being supported (PCC, NCER Parkinson's), a common problem facing biobanks is the lack of visibility of small-scale support to individual research groups, which can lead to an erroneous perception that support is only for the large consortia, or that biobanks are no more than commercial entities. It is important, therefore, to feed back the full range of summary data to as many stakeholders as possible. During discussions, it was stated that multiple requests come in every week, so clearly the maximum spread of stakeholders cannot be involved in the "grid" decisions or the SRC decision – however, the communication could be improved.

The KPIs, as given to the IBBL and presented in the SAR, seem very focused on large-scale national projects, international recognition and economic success/third-party funding. What is lacking is a parallel KPI focusing on the demonstration of the IBBL's value to smaller-scale national research. This new KPI, and its appropriate communication, would be of considerable benefit to the IBBL, reassuring key stakeholders of block grant usage in LU research. It would also reassure potential – but currently

skeptical – stakeholders that the IBBL is supporting medical research, and treating all scientifically relevant requests in a fair and transparent way without commercial gain in mind.

IBBL has a strong management team, under the leadership of Catherine Larue. The committee is under the impression that the CEO has a clear vision on how to achieve IBBL's strategic and operational goals and this vision seems to be embraced by the IBBL staff. Fay Betsou is internationally recognised for her work on biospecimen quality. Sabine Lehmann and Fay Betsou played an important role in the design and the launch of the new ISO 20387 biobank norm. From the evidence presented, the IBBL is recruiting the right staff with an excellent balance of gender, and of age. The training and mentoring of staff below management level is extremely proficient, offering life-long research skills that considerably benefit those who wish to work in industry. Staff are clearly motivated, and all who were interviewed expressed a thorough enjoyment of their work and an appreciation for the excellent staff-management relationships. Without a doubt, the facilities and working conditions are world-class. The ability to explore own research while biobanking is being encouraged as much as possible in the current funding conditions imposed by exterior policy.

The IBBL does not occupy as convenient a physical location as it did before, in terms of the collection of many sample types, but it does benefit greatly from the extra space (which was desperately needed) and an enhanced potential to access diagnostic surplus for cancer collections. To this extent, the current location is appropriate to substantial parts of the IBBL's mission.

Efficiency could be improved by better integration of instruments with databases, and by a robust system of paperless operation. However, these improvements cannot be implemented cheaply without risking the entire functionality and quality of the biobank. Again, in-depth demonstration of spending the block-grant wisely, and in particular on LU research support, should provide useful support for requests for additional funding, if mark-up from external projects is insufficient to cover such re-investment. There is something similar to be said for the need for satellite stations in the main collection centres. A detailed cost-benefit-risk analysis could be explored, versus the current alternative (couriers).

On the matter of finance, a granular and appropriate costing calculator is used to obtain staffing, consumable and equipment costs of projects. However, there is currently no guarantee that overheads (building costs) can be passed on to projects (particularly the external ones) in sufficient quantity to balance the actual overheads incurred annually by the IBBL. Including such overheads might be a useful improvement in the costing models, and could be used to create an advantageous environment for LU projects over external ones. With annual review, at the very least it would demonstrate whether this approach could form a viable long-term proposition, or not.

Finally, this audit noted that Luxembourg, as a whole, lacks sufficient numbers of clinical researchers, and the IBBL would certainly benefit from any policies introduced to remedy this situation.

4 Conclusions

As a summary for the conclusions drawn from the review of the IBBL and described in this report, a SWOT analysis has been prepared (Table 1).

The IBBL is serving its base of clients and the majority of its stakeholders to standards equivalent to very good international practice. It has demonstrated a detailed cost-model with respect to the key components of staff, equipment, and consumables. However, there are areas which could be improved to facilitate enhanced visibility and use nationally, such as the evaluation of overheads, which should be addressed in collaboration with the LIH itself.

The IBBL is clearly a strong player in the international biobanking field (both at the processing and storage level), and among the best in the world with regard to its engagement in biospecimen quality and method standardization. It is managed well, demonstrating appropriate independence and a research focus, public outreach of international standard, and it has extremely competent and motivated staff. The infrastructure and working conditions are outstanding, being well above average on the international scale. These qualities are reflected by customer feedback (the solicitation of which is itself good practice that raises the IBBL above many biobanks), and by return custom.

The main points to improve addressed here relate to the IBBL's integration with the LU research landscape. We think that LU research could benefit to a much higher extent from the services that the IBBL offers, as well as from their international visibility, and so a higher priority should be given towards the support of LU biomedical research, especially in regard to the IBBL's significant Government funding. This shift in prioritisation may be served well by use of a more entrepreneurial approach to charging, such as further offsetting internal contributions against external charges.

The six services that the IBBL offers all run very successfully, as can be seen by increasing number of projects overall, as well as the number of projects per customer, and the uptake of services not traditionally associated with biobanks. As a result, the IBBL foresees that it may eventually be necessary to reject work, if further expansion is not possible. A decision should therefore be taken about which direction is more important to the IBBL's future (expansion or focus of research).

Nonetheless, the Government of Luxembourg should clearly be proud of this exemplary facility.

Table 1 SWOT analysis

Strenghts	**Weaknesses**
• Exemplary quality culture leading the way internationally • International recognition • Independent and research-driven infrastructure • Growing client portfolio • Very happy, motivated and skilled staff • Good management-staff relationship • Outstanding infrastructure and work conditions • Unique biospecimen research effort and proficiency testing programme • Performs above average on the international scale in each of their six biospecimen services • Very satisfied clients • Detailed cost calculation scheme	• Use of block grant not communicated to key stakeholders • Full recovery of overheads not yet implemented • Principles of project prioritization not explained • Automated efficiency metrics not available?
Opportunities	**Threats**
• Be more entrepreneurial with charges levied at LU and external customers • Greater involvement of stakeholders in project prioritization • Consultancy on quality topics, e.g. ISO 20387, as income generator • Luxembourg client mapping to enable a clearer idea of goals • Become “paperless” by integrating equipment into the LIMS system to reduce work load and potential for errors • Engage public even further with summaries of projects supported on the website	• Potential for excessive work load (victim of own success) • Balance between international and national activities • Not all actors in LU accept IBBL’s role

5 Recommendations

5.1 For the IBBL

1. As stated above the main points we raise for improvement are related to the integration of the IBBL in the LU research landscape. We recommend the IBBL to revisit their strategic model and to elevate the importance of LU research over the international partnerships. This should proactively be communicated within the LU research community.
2. Whilst the IBBL's international visibility is very good, which is an important strength of the IBBL, this should be seen and communicated more as a tool to help LU research grow, and not as a mission in itself.
3. We further recommend to communicate information on block grant spending towards stakeholders and improve communication on strategies, project prioritization and sample access policies towards LU researchers. A new KPI should be created to monitor this, focusing on the demonstration of the IBBL's value to smaller-scale national research.
4. To prioritize LU research and clearly communicate so, a simple and openly available pricing system for sample access, sample storage and services that benefits LU over external customers will be helpful. To be clear, this does not necessarily mean increasing its granularity or complexity, but rather, advertising its use – and any 'discounts' – to internal stakeholders.
5. As a further measure to benefit LU research, a generic tissue collection as planned in the Plan Cancer Collection should be started as soon as possible.
6. Further minor recommendations are:
   i) To aim for a better balance of actual vs charged overheads for external customers
   ii) To introduce a new metric on the degree of usage of equipment (e.g. samples processed through automation vs total practical throughput)
   iii) To consider a self-sustainable staff member for consultancy work on quality topics, so that opportunities are not missed
   iv) To work towards a single informed consent document for studies acquiring biosamples, so that samples from different studies can be combined for projects later on
   v) To make a decision whether future expansion, or future research focus, is more important to the IBBL

5.2 For the Ministries

7. There are a couple of recommendations that go beyond those that the IBBL can implement by itself. During discussions, it was clear that the number of clinical researchers is believed to be having a detrimental effect on the quantity of research possible. The Ministries might therefore wish to consider what policies could be introduced to increase the number of clinical researchers active in LU.
8. There is also the matter of biospecimen research. It is a deceptively niche area of science, consequently overlooked on an allegedly systemic basis. However, its potential to uplift the value of medical research is considerable. The Government might therefore wish to consider how it could change FNR funding rules, in order to enable more biospecimen research that, in turn, would benefit future basic research, translational work, and clinical studies.

Appendix A Members of the Assessment Committee

Dr. Gabriele Anton is head of the biobank group at the Institute of Epidemiology at Helmholtz Center Munich. The biobank is a major resource for researchers working in the fields of prevention, diagnosis and therapy of complex diseases and collects biosamples since more than 30 years. Currently the group is establishing the Core Facility HMGU Biobank that will offer services around biobanking to all institutes at Helmholtz Center Munich and collaboration partners.

Gabi received her PhD from the Ludwig-Maximilians-University (LMU) Munich in 2000. Her postdoctoral work focused on infection research. Today she is involved in national and European projects in the field of biobanking, for example within the German Center for Infectious Diseases, in the German Biobank Alliance and in BBMRI-LPC (Biobanking and BioMolecular resources Research Infrastructure – Large Prospective Cohorts).

Dr Gareth Bicknell is the Operations Manager at the University of Birmingham's Human Biomaterials Resource Centre, a research tissue bank licensed by the UK Human Tissue Authority and running under generic research ethical approval. Prior to Birmingham, Dr Bicknell was the Quality Manager/Acting Manager at the University of Oxford's HTA-licensed musculoskeletal biobank, where he developed existing quality systems for nearly four years.

Dr Bicknell received his PhD from the University of Leicester in 1996. After eight years of postdoctoral work, he concentrated on management of a licensed human tissue-processing facility for transplant, and a separate renal transplant research laboratory. He also assisted the UK HTA perform its first round of regulatory inspections, gaining valuable insight into regulatory mindset. Since 2016, he has been an active contributor to the new ISO 20387 standard for biobanking.

Appendix B Site visit programme

Day 1 – September 12 – Room LNS 0213 Louis Pasteur

Time	Programme	Participants*
08:30 – 09:00	• Transfer to IBBL: Dudelange, 1, rue Louis Rech	Peers and Technopolis
09:00 – 11:15	• General introduction to IBBL (Catherine) (and critical self-assessment of IBBL); discussion	IBBL management team, Estelle Sandt
11:15 – 12:30	Tour around IBBL	Fay Betsou, Dominic Allen
12:30 – 13:30	(Simple) Lunch	IBBL management team, Estelle Sandt
13:30 – 15:15	• Presentation and discussion on theme 1 '**Biospecimen research**', based on max. 30 min. short presentations followed by discussion - Biospecimen research and liquid biopsy – 10 minutes (Wim) - Biospecimen research and quality control tools for blood derivatives – 10 minutes (Olga) - Biospecimen research and tissue – 10 minutes (Bill)	Wim Ammerlaan, Olga Kofanova, William Mathieson by skype, Estelle Sandt
15:15 – 15:30	Tea/coffee	
15:30 – 17:15	Presentation and discussion on theme 2 '**IBBL's involvement in large national programme'.** IBBL will present : - a case study on colorectal cancer (SOCS) – 15 minutes (Christelle) - a case study on the National Centre for Excellence in Research on Parkinson's Disease (NCER-PD) – 15 minutes (Estelle)	Christelle Bahlawane, Estelle Sandt
17:15 – 17:30	Tea/coffee	
17:30 – 18:30	Informal group meeting (with e.g. PhD students or trainees)	Lorieza Castillo, Kathleen Mommaerts, Monica Marchese, Sonia Garcia Frasquilho, Gaël Hamot
18:30 – 19:00	Draft conclusion of the first day	Peers only
19:00 – 20:00	Transfer to hotel, free time	Peers and Technopolis
20:00	Dinner	IBBL management team, Estelle

* Peers and Technopolis will attend all sessions

Day 2 – September 13 Room: LNS 0213 Louis Pasteur

Time	Programme	Participants*
08:15 – 08:45	Transfer to IBBL: Dudelange, 1, rue Louis Rech	Peers and Technopolis
08:45 – 10:30	Presentation and discussion on theme 3 **'IBBL's involvement in large international project'.** IBBL will present a case study on the following projects: - European Organisation for Research and Treatment of Cancer (EORTC) - 10 minutes (Angela) - Proficiency Testing from Day 1 - 10 minutes (Amélie) - Cancer ID (Wim)	Angela Hogan, Amélie Gaignaux, Wim Ammerlaan, Estelle
10:30 – 10:45	Tea/Coffee	
10:45 – 11:45	• Time scheduled for meeting clients/partners of IBBL	Clients/partners of IBBL : Serge Haan, university of Luxembourg (SOCS project) Debora Fumagalli (BIG)
11:45 – 12:15	• Time reserved for clarification of questions from the peers	IBBL management team, Estelle
12:15 – 13:15	(simple) Lunch	Peers
13:15 – 14:45	• Time to draft preliminary conclusions	Peers
14:45 – 15:00	Tea/coffee	
15:00 – 16:00	Presentation of preliminary conclusions and discussion on possible recommendations	IBBL management team, Ministery of Higher Education and Research, Ministery of Health and others
16:00	End of programme, transfer to train station/airport	

* Peers and Technopolis will attend all sessions

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