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The CM-Path Biobanking Sample Quality Improvement Tool: A Guide for Improving the Quality of Tissue Collections for Biomedical Research and Clinical Trials in Cancer

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Author contributions: CM-Path management (KO, AH); Developed content of the Biobanking Sample Quality Improvement Tool (VS, JH, RT, AH, GT); Developed the online tool and coordinated the pilot phases (HF, HP)**;** Wrote manuscript (VS, AH, GT)**;** Read and approved final version (All)

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Tenovus Cancer Care. These organisations did not participate in study design; collection, analysis and interpretation of data; writing the report or the decision to submit the paper for publication.

Abstract

Biobanking is now a key discipline in cancer research and its infrastructure. This helps accelerate translational research and is typically pathology-led. To use biobanked tissues to best effect, sample quality is paramount, and biobanks have a responsibility to ensure this is achieved. In 2016, the National Cancer Research Institute (NCRI) established the Cellular & Molecular Pathology initiative (CM-Path), which aims to re-invigorate UK academic pathology in the UK. One of the goals of the CM-Path biobanking subgroup group was to create a Biobanking Sample Quality Improvement Tool. The tool is a confidential self-assessment of current practices within a biobank, focusing on tissue quality and identifying areas with the potential for improvement. Here we describe the development and implementation of this tool and discuss what it can offer to the cancer biobanking community.

Introduction

Good quality tissue samples are essential to drive translational research and can be obtained from biobanks. Biobanking has gradually evolved from 'private' collections, usually initiated by academics or commercial companies with interests in specific disease types, into a discipline in its own right enabling translational research allied to laboratory and clinical investigations, or as an adjunct to clinical trials. Whilst requiring engagement by all members of the multi-disciplinary team, pathologists remain central to this, and best practice biobanking, at least in cancer, should have input from appropriately skilled pathologists.

Biobanks now exist across the world. Many operate according to strict Standard Operating Procedures (SOPs) with global (ISBER (International Society for Biological and Environmental

Repositories); https://www.isber.org/), European (BBMRI-ERIC (Biobanking and BioMolecular Resources Research Infrastructure-European Research Infrastructure Consortium); http://www.bbmri-eric.eu/) and national (CTRNet; Canadian Tissue Repository Network; http://www.ctrnet.ca/) frameworks developed. The National Cancer Research Institute (NCRI), established as a UK-wide partnership between cancer research funders, recognised the need for better harmonisation and greater coordination between biobanks and established the Confederation of Cancer Biobanks (CCB; https://cmpath.ncri.org.uk/ccb/) in 2006. The goal of the CCB was to share best practice and raise awareness of existing sample collections with researchers, so that tissues donated by patients could be used to best effects. In 2016 the (NCRI) Cellular Molecular Pathology (CM-Path) initiative (https://cmpath.ncri.org.uk/) was established as a means of strengthening the academic pathology base across the UK to enhance pathology-led research (1). Within this structure a separate biobanking sub-group was established. Subsequently, the CCB was incorporated into CM-Path with CM-Path continuing the work initiated by the CCB.

Issues with tissue samples for cancer research may relate to quality and quantity. It is recognised that, following excision from patients, tissues are subject to widespread variability in conditions encountered during their journey to the biobank and onwards to research laboratories, at both the pre- and post-acquisition stage. Variables like ischaemic times, sample handling, storage, distribution etc., may adversely affect tissue quality, potentially impacting on data generated. Several publications have described degradation of protein epitopes because of fixation delay, with phosphoproteins particularly susceptible (2-4). Sometimes it may be necessary to obtain tissue from multiple biobanks in order to accrue sufficient numbers of samples to capture the full disease spectrum. Registries of biobanks exist in the UK (https://www.biobankinguk.org/) and Europe, with the BBMRI-ERIC Directory 2.0 listing > 60 million samples from 515 biobanks or individual collections (5), which can help researchers identify and source suitable tissues. However, unless biobanks are

working to equivalent standards and quality management, variability in tissue collection protocols may compromise research results, which may raise questions regarding sample consistency (6, 7). The old adage "garbage in garbage out" applies acutely to biobanks. To mitigate this, the Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines were established, providing information on consistency of collection, processing and storage of human tissues, with an emphasis how to report these in research publications (8), however this does not appear to be adopted widely.

One of the goals of the CM-Path biobanking subgroup was to develop, pilot and implement a Biobanking Sample Quality Improvement Tool to help biobanks identify factors which could improve tissue quality, and consequently, data output, for researchers. Here we describe this tool and discuss what it can offer to the biobanking community.

Methods

Development

Through various Working Groups, the CCB had previously established and agreed a set of quality standards ("Guiding Principles") to be adopted by biobank staff, to provide assurance on the value of the samples and data that they held (http://cmpath.ncri.org.uk/wp-content/uploads/2019/06/CCB-Guiding-Principles-v7.pdf). These were used as the basis for developing the Biobanking Sample Quality Improvement Tool. An initial scoping phase involved phone consultations between the project coordinator (HF) and various specialists in biobanking (named in the acknowledgments) to determine the need for such a tool. Subsequently, each member of the CM-Path biobanking subgroup (AH, JH, VS, GT), all biobankers with significant experience in conducting and supporting translational cancer research across different tumour types were assigned to develop a specific section of the Biobanking Sample Quality Improvement Tool. Patient input was provided by RT. They

worked closely with HF through phone consultations and email to develop a series of questions. Subsequently, these data were shared with other members of the CM-Path biobanking subgroup and refined further through an iterative process via fortnightly teleconferences and email. Links to relevant literature were identified and incorporated into the tool to assist end users. The tool was designed, such that upon completion, a report could be generated to flag up areas of attention the biobank staff may wish to consider. Once agreement was reached, this information was used to populate the Biobanking Sample Quality Improvement Tool~~Biobanking Self Improvement Tool~~. To promote ease of use and of access, we designed the Biobanking Self Improvement Tool using Microsoft Excel, a commonly used software package with widespread availability. The tool can be downloaded, free of charge, at: http://bit.ly/CM-Path_biobanking. The dashboard for the tool is shown in Figure 1.

Pilot phase

The tool was piloted across four UK biobanks, selected to provide diversity in collections and funding models as well as a good geographical spread: Greater Glasgow & Clyde Biorepository (multiple cancers; government funded; Scotland), Leeds Breast Cancer Now Tissue Bank (breast cancer tissues; charity funded) and Multidisciplinary Research Tissue Bank (mainly renal, colorectal and gynaecological cancers; charity, research council funded; North of England) and Southampton Tissue Bank (multiple cancers; charity, research council funded; South of England). Opinions were sought from biobank staff at these centres on the usability of the tool and suggestions for improvements encouraged prior to its launch to the biobanking community. Participants who piloted the tool were independent, but they were located at the sites of the creators of the tool.

Post-launch phase

After the tool had been operational for several months, opinions were sought from users on general impressions, any technical difficulties, if the tool highlighted areas in end user's organisation that required attention, suggestion of areas for improvement and who would benefit from using the tool.

Results

Pilot phase

Initial general feedback at the piloting phase was encouraging:

"Overall this looks like a really useful tool. It was straightforward to use, and I found the links to research and example forms useful."

"The CM-Path biobanking tool is very professionally laid out and easy to use. The tabs are useful and logical."

"Easy to navigate around. Bold bright colours and nice layout."

Participants in the pilot gave more specific feedback, highlighting several operational issues with the tool to ensure that the whole spreadsheet was functioning as it should. For example, ensuring drop down boxes were functional and that the correct text came up relating to the right question. They also checked the wording to make sure this didn't across as confrontational, judgemental or off-putting to ensure it was being used purely as an educational tool. These were addressed prior to launch. Participants felt the tool would be valuable for internal auditing of established biobanks and useful when setting up new biobanks to ensure SOPs were in place and that the correct guidelines were being followed. They also highlighted its use for all biobank staff, as it could provide everyone with confidence in quality of the samples they have collected and stored for research.

Launch

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The Biobanking Sample Quality Improvement Tool ~~The Biobanking Self Improvement Tool~~ was launched to the UK biobanking community at a workshop held in Leeds, England on 16 May 2018. Upon clicking on http://bit.ly/CM-Path_biobanking users are taken to the CM-Path home page within NCRI. To download the tool, users are asked to enter name, email address and organisation with a yes/no option for future contact regarding providing feedback on the tool. A link to copy and paste into a browser then appears and the tool is downloaded as a zip file. Once unzipped, this opens as an Excel spreadsheet (Figure 1). Users may access topics related to sample acquisition, storage, transport and standard operating procedures, either as tabs or radio buttons. When these are clicked, a series of questions related to each topic appear. These are completed by selecting the appropriate answer from a dropdown menu. After each response a commentary and/or evidence appears explaining why the subject of the question is important with respect to the quality of samples being stored, often linking to additional reading. Where answers indicate there could be room for improvement, suggestions can be found in the tab 'flagged areas' and the 'links' tab offers relevant information from other sources. These are tailored to the responses provided by users. By 1 November 2019 the tool had been downloaded 81 times from 12 countries (UK x40, France x2, once each from Austria, Belgium, Denmark, India, Ireland, Saudi Arabia, Ukraine). There were 32 downloads from unknown locations or countries as the people downloading did not disclose their organisation or location. At least five downloads were from industry, one pharma company, several charities and university/NHS hospitals across the UK and beyond.

Discussion

As we move towards personalised approaches to medicine, which requires access to high quality human tissue samples, improvements in biobanking are very much on the agenda to help ensure that sample quality meets the expectations of researchers.

There have been international efforts towards biobanking self-improvement. The Canadian Tissue Repository Network (CTRNet) developed and implemented a set of required operational standards, which all biobanks in their network had to adhere to in order to gain CTRNet certification (6). This was endorsed by ISBER (7). More recently a biobank certification scheme has been developed in Australia (9). This took the operational costs of running a biobank into consideration and set guidelines for best practice management of collected materials in biobanks and benchmarks for subsequent certification. The Australian model also accounted for resources required to obtain and maintain certification, with biobanks employing the highest numbers of staff reporting the lowest anticipated costs in gaining and maintaining this (9).

While these are undoubtedly positive developments, development and implementation of an informative, user-friendly tool designed to support the improved quality of samples donated to UK biobanks was lacking. Our tool has bridged this gap. Feedback from the community has been positive and uptake has been steady with 81 downloads since its launch. Interestingly this has included users from beyond the UK, with downloads from as far afield as Ukraine and Saudi Arabia, demonstrating a wider reach. A frequent comment was how useful the tool would be for new members of staff or for those who were new to the biobanking field as well as offering a checklist to ensure that biobanks are covering important aspects of sample quality and ensuring robust SOPs are in place following the correct guidelines and science.

We acknowledge that other tools are available which address sample quality in biobanks, notably ISBER, College of American Pathologists (CAP) and BBMRI-ERIC. ISBER offers suite of tools on their website (https://www.isber.org/) but much of this is restricted to members only, notably their Self-Assessment Tool. The ISBER website also signposts freely available information e.g. https://www.findmyassay.com, which provides a guide to identify if previously collected tissues are

fit for purpose for a range of experiments methods. CAPs Biorepository Accreditation Programme (10) employs peer-based inspections to accredited biobanks enrolled on their programme. Accreditation is over 3 years, obtained through application, annual enrolment fee and submission of information on the activities of the biobank, followed by on-site peer inspection in the first year, then self-inspection plus CAP desk assessment in the second and third years. BBMRI-ERIC's ISO 20387:2018 Biotechnology – Biobanking - General requirements for biobanking is a comprehensive document, conforming to ISO standards, however it is behind a paywall of $160 / €150. Importantly, our ~~the~~ tool is free and accessible for everyone, using a commonly used Microsoft platform which builds on areas already covered by current relevant UK legislation set by the Human Tissue Authority and Healthcare Improvement Scotland. It offers an internal self-assessment of current practices, focusing on tissue quality and identifying areas which could be improved and although developed in the UK, has applicability to biobanks everywhere.

The focus here has been on the quality of tissue samples within biobanks, however we recognise the need for good quality data to accompany these samples to derive most benefit from them. Informatics and data management aspects of biobanking are discussed elsewhere (11-14).

In summary, the CM-Path Biobanking Sample Quality Improvement Tool offers a free and confidential way for biobanks to work towards improving their standards. We encourage the community to view this tool and to consider implementing this into their workstreams.

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Table 1

Summary of points raised by users of the CM-Path Biobanking Sample Quality Improvement Tool

Questions	Responses
General comments	• Using the different tabs and answering the questions is very straightforward • Covers a wide range of specific questions that we should all be asking regarding sample collection and processing
Value of the tool	• Good for internal auditing of banks • Useful when setting up new sites/ new tissue banks: making sure all SOPs are in place and are following the correct guidelines and science • Checklist to ensure that banks are covering every aspect of sample quality • Following set standards could help inform cost recovery • Very useful for anyone considering setting up a bank • Useful for established banks who want to tighten up processes
Ease of use	• Very easy and quick to use (around 20 mins) • Self-explanatory • Helpful that can jump forward to certain areas according to area of interest or specific SOPs
What specific areas of the tool are important?	• All aspects of the tool are important • Flagged areas are most important as these indicate what could be changed to improve

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	• Reminder to ensure that ischemic times, freeze thaw cycles and time in fixative are all recorded are particularly important • Lot of useful links provided for further exploration
What areas of quality could potentially be improved by use of the tool?	• Sample quality, particularly for certain techniques • Tool offers ability to evidence quality of samples and processes
Who in the biobank would benefit from the tool?	• All personnel, as it provides everyone with confidence/knowledge of the quality of samples they have stored and are giving out • Manager/head of biobank would be able use it for audit and checking status of SOPs • Excellent for new staff to help understand why specific tasks are performed and recorded • Add to the list of resources for new staff joining the biobank so everyone is on the same page
How could the tool be improved?	• Better if the questions had more options as not everything has binary answers • Consider sections on collection of blood derivatives • Revisit the tool periodically to keep it updated as new methods emerge and its use evolves

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Figure legend

Figure 1

Dashboard for the Biobanking Self Improvement Tool. Users are presented with a series of tabs on topics related to sample acquisition, storage, transport, and standard operating procedures, which expand to show a series of questions related to the topic. Once completed, suggestions for improvement can be found in the tab 'flagged areas' and the 'links' tab offers relevant information from other sources.

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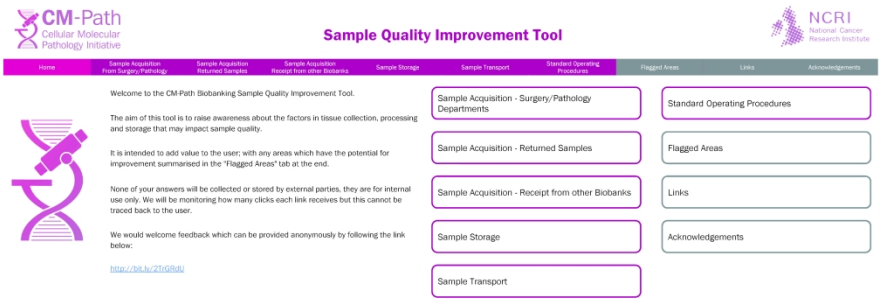

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