The Availability of Human Biospecimens to Support Biomarker Research

Biomarker Insights
Volume 17: 1–8

DOI: 10.1177/11772719221091750
SAGE

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ABSTRACT: Preserved biospecimens held in biobank inventories and clinical archives are important resources for biomarker research. Recent advances in technologies have led to an increase in use of clinical archives in particular, in order to study retrospective cohorts and to generate data relevant to tissue biomarkers. This raises the question of whether the current sizes of biobank inventories are appropriate to meet the demands of biomarker research. This commentary discusses this question by considering data concerning overall biobank and biospecimen numbers to estimate current biospecimen supply and use. The data suggests that biospecimen supply exceeds current demand. Therefore, it may be important for individual biobanks to reassess the targets for their inventories, consider culling unused portions of these inventories, and shift resources towards providing prospective custom biobanking services.

KEYWORDS: Biobanks, Inventory, Utilization

RECEIVED: February 2, 2021. **ACCEPTED:** March 15, 2022.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Biomarker discovery, translation and validation in health research all depend on different types of biospecimen resources that enable the generation of data that are considered to provide distinct levels of evidence.[1,2] In general terms, biomarker discovery depends on availability of relevant biospecimens in flexible formats appropriate for interrogation using a range of assays; biomarker translation depends on availability of biospecimens and data in the context of retrospective cohorts selected to be representative of specific clinical situations; and biomarker validation depends on availability of prospective patient cohorts assembled under specified criteria with associated biospecimens and outcomes data.[3]

Retrospective biospecimen cohorts necessary for biomarker discovery and translation mostly come either from research collections (ie, inventories of the many types of research biobank[4,5]) or from clinical archives.[6] The biospecimens are typically tissue or blood samples that are mostly preserved in either a frozen format (tissue and blood in biobank inventories[7]) or a fixed format (formalin fixed and paraffin embedded tissues in clinical pathology archives[8]). However, the preferred source of retrospective tissue biospecimen cohorts has changed. Frozen format tissue biospecimens were essential for many of the research assays deployed in the 1980's and 1990's, and this provided the motivation for the development of biobanks in health research, with their extensive inventories.[9] Since then the development of several high throughput technologies, combined with both analytical and bioinformatic approaches, have increased overall demand for all biospecimens.[10,11] This has provided a stimulus for increased access to fixed tissues in clinical archives for retrospective studies.[12,13] At the same time, there has been a recent increased demand for prospectively collected fresh tissue and blood samples,[14,15] possibly attributable to the increased interest in the function of the immune system in health research. Collectively these trends have led to diminished demand for frozen biospecimens in biobank inventories (Figure 1). So, while there is continued increase in demand for biospecimens for biomarker research across the spectrum from discovery to validation, the changes in demand for the types of biospecimens in biobank inventories means that we should ask the question, "are there enough, too few, or too many biospecimens in research biobank inventories to support biomarker research demand." If there are too few of the right types of biospecimens, we should recognize this and consider how to rectify the situation. If there are too many, then it is possible that resources could be freed up from maintaining excessive collections.

This commentary will address this overall question through consideration of a series of preliminary questions that need to be examined to allow us to estimate supply and demand of biospecimens.

Biospecimen Supply and Demand

Definitions and limitations

Before diving into these questions around biobanks and their biospecimens, it is important to define the units of measure. The National Cancer Institute Best Practices for Biospecimen Resources defines human biospecimen resources as encompassing all types of specimen collections and data for research

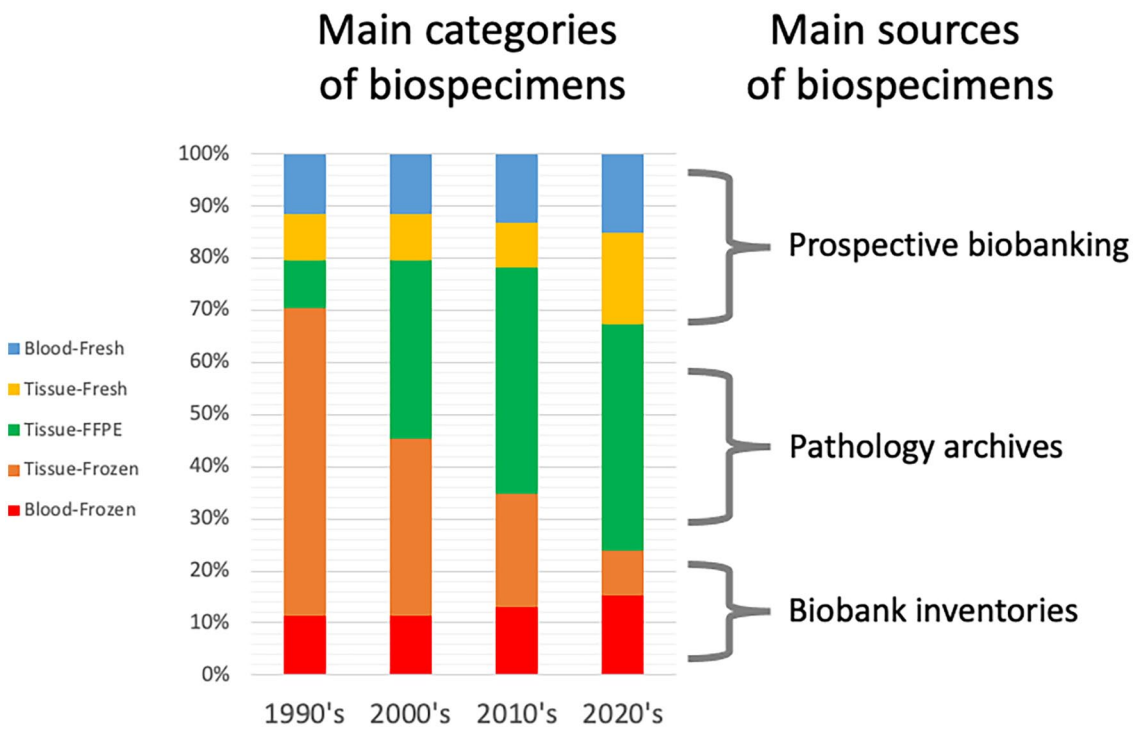

Figure 1. Schematic of changes in the proportions of major human biospecimen categories and the main sources of these biospecimens used by biomarker research over 4 decades. Major biospecimen categories described in terms of type and preservation formats include fresh, formalin fixed paraffin embedded (FFPE), and frozen tissue biospecimens and fresh and frozen blood biospecimens. The main sources of these biospecimens are indicated as follows; prospective biobanking (fresh tissue and blood), pathology archives (FFPE) and biobank inventories (frozen tissue and blood).

purposes and includes the facilities, policies and procedures inherent to biobanking operations.[16] Consistent with this definition, a human health research biobank is considered here broadly as an entity that comprises a collection of biospecimens and data created in the course of a research project, study, or trial. Using this definition there are many types of biobank, but we will limit the focus here to academic biobanks, both small and large, with 'classic' operating models and inventories of biospecimens supporting academic health research.[17,18] Biospecimens and associated data are the main products of these academic biobanks. The biospecimens are obtained from a donor and the data is either derived from the donor, from the management of the biobanking process, and/or from the data generated from analysis of biospecimens. We will also focus mostly on biobanks storing intact biospecimens as opposed to collections of nucleic acids derived from processing biospecimens. However, there are many types of biospecimens that can range from whole organs to small tissue blocks or thin sections of tissue or small volumes of fluids or fractions of these fluids, and many layers of granularity to the associated data. No consistent terminology or approach to denote size or volume of biospecimens (or extent of data) has been widely adopted in health research, as reflected in the several alternative terms (including; specimens, tissues, samples, blocks or aliquots) commonly used to indicate biospecimens. Therefore, we acknowledge that there are challenges in defining the numbers of biospecimens in a biobank and comparing these between different biobank inventories based on this lack of consistent terminology. However there are some relatively common and widely used approaches to processing some types of tissues (eg, cancer biospecimens) and fluids (eg, blood samples) that creates some consistency and supports comparisons.[19-21] These processing approaches lead to the creation of relatively standard sizes of biospecimens for storage (eg, frozen tissues in 1.5 ml cryovials and frozen blood plasma and serum fractions in 500 ul-2 ml volumes[7,22-24]) that are usually the basis of reported overall numbers of biospecimen units reported by biobanks. There are also similar challenges in making comparisons of numbers of biospecimens used for research. Publications listed in large online databases (eg, PubMed) provide the best data source to determine biospecimen use in research. However no standard terminology is used to indicate use of human biospecimens in papers, and no commonly defined data elements have been widely adopted to indicate the source, size or volume of biospecimens utilized.[25,26] Furthermore, not all biospecimens used in research generate data that is reported in publications. However a reasonable estimate of the numbers, patterns and trends in biospecimen use in publications can be obtained by careful review of papers using defined search criteria.[6]

Biobank inventories

There is no mandated requirement to register all forms of biobanks or their biospecimen collections in any country. This makes biobanks hard to find.[27,28] Therefore in the past, attempts have been made to survey multiple data sources to identify

Table 1. Details of the current number of biospecimens reported by each of 5 representative large biobanks in British Columbia, Canada (top part of table) along with a calculated average of the estimated number of biospecimens per million population in this region based on these biobanks (bottom part of table). Definitions for large biobanks (>1000 participants), and medium-small biobanks (⩽1000 participants) are taken from O'Donoghue et al.[31]

	BIOBANKS[a]	PURPOSE[a]	# CASES	# BIOSPECIMENS	# BIOBANKS/M[c]	# BIOSPECIMENS /M[d]
BC examples	BC Generations	multipurpose	30 000	122 000	–	–
	CVTR	cardiovascular	15 000	100 000	–	–
	Predict	cancer	13 000	79 000	–	–
	TTR	cancer	6400	46 000	–	–
	JHLTR	lung	3000	40 000	–	–
BC averages[b]	Large	–	13 000	77 000	2	154,000
	Small-Medium	–	200	500	20	10,000
	All biobanks	–	13 200	77 500	22	164,000

[a]Selected biobank examples, and the purpose with respect to the area of health research supported, are as follows; BC Generations = BC Generations cohort biobank (https://www.bcgenerationsproject.ca), CVTR = Cardiovascular Tissue Registry (https://www.hli.ubc.ca/our-services/cardiovascular-tissue-registry), PREDICT = Victoria Cancer Center blood biobank (http://www.bccancer.bc.ca/our-research/research-focus/engaging-patients-in-research), TTR = Tumour Tissue Repository (https://www.bccrc.ca/services/biobanking-biospecimen-research-services-bbrs), JHLTR = James Hogg Lung Tissue Registry (https://www.hli.ubc.ca/our-services/lung-tissue-registry).
[b]Large biobanks, ⩾1000 biospecimens; Small-Medium biobanks <1000 biospecimens.[31]
[c]# biobanks/M, number of biobanks per million population based on the current population of British Columbia (https://www2.gov.bc.ca/gov/content/data/statistics)
[d]# biospecimens/M, number of biospecimens per million population based on the average numbers of biospecimens in the examples of biobanks in British Columbia.

biobanks[29] and to estimate overall numbers of biobanks and biospecimens across sectors and institutions.[30] More recently we have taken the opportunity presented by several mature online biobank locators to address some of these questions.[31] There are many types of online locators but some have defined the type and location of biobanks within regions for inclusion, achieved some maturity and are associated with some positive pressure (eg, funder requirements and mandates) on biobanks to enrol.[32-35] Therefore, we have used these locators to estimate the number of biobanks within defined regions. We concluded that across regions with potential for high research capacity, as indicated by comparable Gross Domestic Products (GDPs), there are approximately 2 large biobanks with >1000 samples and a further 9 to 28 medium-small biobanks with 201-1000 or 1-200 samples per million population.[31]

Nevertheless, the information on inventory sizes within these locators is often general, in that some locators use different size categories and definitions for categories based on biospecimen numbers and some are based on patient case numbers. Therefore, to translate the number of biobanks per million population into numbers of biospecimens in the inventories, it may be more accurate to extrapolate from a set of representative biobanks from a defined region. Here, we will consider biobanks in the region of British Columbia Canada (total population 5 million), including a representative set of large biobanks, with which one of the authors (PW) is directly familiar. These biobanks have been in operation for between 10 and 40 years, comprise population cohort[36,37] and disease focused biobanks,[38-40] and represent biobanks supporting a range of health research.[36-40] The disease focused biobanks comprise either blood[37] or tissue collections[38] to support cancer research, and cardiovascular tissue[39] and lung tissue[40] collections that support health research in these respective areas. Details of the current number of biospecimens reported by each biobank are shown in Table 1, along with a calculated average of the estimated number of biospecimens per million population in British Columbia. This calculation also incorporates an estimate of the number of biospecimens held in small-medium sized biobanks, using the midpoint of the range of the estimated number of these other biobanks. This analysis, which estimates an average number of ~164 000 biospecimens stored in biobank inventories per million population, is based on data from only 1 province. However the total annual investment in health research in British Columbia is very close to the national average on a per capita basis ($13 vs $12 per person over the 4 year period 2008-2012) across all regions of Canada.[41] It is therefore reasonable to assume that the average number of ~164 000 biospecimens stored in biobank inventories per million population is applicable to Canada and other countries with a comparable GDP and health research enterprise.

Biobank inventory utilization

Current demand for biospecimens and utilization can best be deduced from an analysis of biospecimen use in published literature. We have previously conducted several different studies to assess trends in biospecimen use in health research over the past couple of decades.[10,42,43] Most of these studies were concentrated on cancer research and looked at utilization from the viewpoint of selected individual research labs, research funders

and journals.[10,42,43] However our most recent study in this area was directed more broadly to publications across all health research using a randomly selected cohort of 225 papers published over 2 decades from 2000 to 2020.[6] While the primary focus was on the assessment of the trends in the complexity of biospecimens and their associated data used in health research, the study also generated data on the sources and numbers of these biospecimens used. In 2020, the most recent period analysed, the average numbers of total biospecimens used in each paper was 204 and 1/5 of collection pathways for biospecimen cohorts involved biobanks, and 14% overall were retrospective cohorts (ie, most likely drawn from frozen biospecimens in biobank inventories).[6] The other 4% of cohorts involving biobanks were prospective cohorts (ie, most likely fresh biospecimens collected for the study by a biobank).[6]

In order to express biospecimen utilization in the same terms as our estimate of supply, it is necessary to calculate the numbers of researchers per million population and their publication output. We will again draw on estimates for the number of health researchers in Canada and their typical annual output of publications utilizing biospecimens. The Canadian Institutes for Health Research has estimated in 2018 that there are 13 000 researchers from all pillars of health research in Canada.[41] This translates into ~350 health researchers per million population in Canada. The typical annual output of publications utilizing biospecimens from these researchers can be estimated at 1.2 papers per researcher per year.[44] This output estimate is based on a small but nationally representative group of cancer researchers assessed in a previous study of the publication output of Canadian cancer researchers funded by a national cancer research agency in 2011.[44]

An estimate for current utilization rates from biobank inventories (demand) in Canada can be summarized in terms of total biospecimens used per year in retrospective cohorts drawn from biobanks and reported in publications by researchers. This estimate is calculated as follows; 204 biospecimens per average paper[6] × 14% of biospecimen cohorts used are retrospective and from biobanks[6] × 1.2 papers using biospecimens are generated by a researcher per year[44] × 350 researchers per million population[41] = ~12,000 biospecimens per million population.

The current overall balance sheet for supply versus demand for biobank inventories in Canada is therefore approximately 164 000 biospecimens per million population stored in biobank inventories versus 12 000 biospecimens per million population used per year for research, which equates to a ratio of 13:1.

Uncertainties and Projections

As already noted, there are several uncertainties on both sides of the balance sheet that could change these estimates of supply and demand. There are also several factors that might influence the balance in the future.

These initial estimates are based on extrapolation from relatively limited datasets within a few small studies.[6,42,44] The limitations are in terms of accurate biobank numbers, definitions underlying reported numbers of biospecimens, estimates of average sizes of inventories and details restricting the extent of analysis of utilization of biospecimens to research papers across all areas of published health research.

The estimate of current supply at ~160 000 biospecimens stored/million population in Canada is lower than the estimates previously suggested for the US in 2000[30] and 2012 but is very comparable to the projections based on more recent data from Europe[45] (Table 2). However the US estimates included processed derivatives such as nucleic acids as well as intact biospecimens and the European estimate may be conservative, as many small-medium sized biobanks are not represented in the directory.[45] Differences in the scale of the health research enterprise, as reflected by overall GDP per person (USD) in each region (European Union 34, Canada 44, USA 64)[46] may also influence these numbers.

The estimate of current demand at ~12 000 biospecimens used each year per million population may be influenced by the density of health researchers in Canada and the specific sector of health research under consideration. For example, cancer research has been at the forefront of health research in terms of discovery and translation of biomarkers into practice[47] and may have higher demands for biospecimens. In addition, in many cases, biospecimen use reported within papers may not reflect all the biospecimens used in the research laboratory, for example in preliminary assay development and validation steps or in generating unpublished data. Biospecimen use in research supported by industry is also probably under-represented in the published literature. Perhaps more importantly, the number of biospecimens used to support any given study may relate to only a very small fraction of the individual biospecimen or aliquots of this biospecimen stored within a biobank inventory. Each biospecimen is often subdivided and stored as several blocks or aliquots[22,24] and only fractions of these blocks and aliquots (eg, limited numbers of thin tissue sections from tissue blocks or small portions of fluid aliquots) may be used from a biobank for each study.[48] Also, as illustrated in Table 1, large biobanks may hold many biospecimens per case.

Many factors may change these current estimates in the future. Our previous studies, focused on cancer research papers alone, have consistently identified a relatively steady proportion (~40% of all publications[42,44]) that utilize biospecimens to generate at least some of the data reported. However we have also observed continuing trends towards increased biospecimen cohort sizes used in individual papers,[42,43] which would be expected to continue to increase the scale of annual demand for biospecimens. Furthermore we have also seen changes in the dominant preferences in preservation formats for tissues, most recently from frozen format to FFPE tissue format, which would be expected to have an opposing effect and to reduce some demand for frozen tissue from biobank inventories.[42,43]

Table 2. Estimates of the total number of specimens stored in research biobank inventories in different countries and regions. The estimates for the United States of America and the European Union are derived from the sources listed and for Canada is extrapolated from data from British Columba (see table 1).

SOURCE	COUNTRY/REGION[a]	YEAR[b]	# OF SPECIMENS[c]	POPULATION[d]	# SPECIMENS/M[e]
Eiseman[30]	USA	2000	120M	285M	421,000
Henderson[29]	USA	2012	210M	314M	669,000
Holub[45]	EU	2016	60M	445M	135,000
	Canada	2020	6M	38M	164,000

[a]USA = United States of America; EU = European Union
[b]Year in which the study or survey or estimate was conducted.
[c]Number of specimens in millions (M). Note that USA and EU estimates include extracted biological derivative specimens such as nucleic acids as well as biospecimens.
[d]Population in millions (M). Data from www.data.worldbank.org.
[e]Number of specimens per million population

Debating the balance sheet

Does a ratio of 13:1 for stored versus used biospecimens represent too much supply or too little demand, or both? In other words, are there too many biospecimens that are never selected for retrospective biomarker studies held in biobank inventories, or are too few biospecimens applied for or made available by restricted access biobanks? This question and the many factors that might impact the conclusion, remain to be debated by all stakeholders. However, some initial comments to ground this debate will be offered here.

The question of underutilization of some biobank inventories has surfaced in the past[29] and the conclusion was drawn that low utilization indicates an oversupply.[49] But as delineated in a recent set of papers,[3,17,50-52] while individual biobank utilization rates are very variable, these rates are also hard to judge as good or poor, because they are affected by many factors.[3,17,52] Nevertheless when biobanks with similar designs and operational models are compared, low utilization rates can be an indicator of performance.[3,53] In these cases, low utilization may arise because of low visibility of the biobank for researchers, or restricted biobank access policies, or just poor and/or obsolescent planning.

However low utilization can also reflect the maturity of the biobank. Much of the value in utilizing retrospective cohorts of biospecimens lies in the ability to link research findings with clinical outcomes data (eg, data related to the response of the donor to treatment).[54] In cancer research the operational design of many 'classic tumour biobanks' involves collection and then storage for many years before intended use occurs.[17] At the time of intended use it is anticipated that specific research questions will require selection of specific subsets of patients and associated biospecimens from the collection that meet defined section criteria. Therefore inventories, by design, need to be maintained without exhausting biospecimens for some time and inventories need to be larger than the forecasted demand to allow for case selection.

Many of the inventories that we have referred to here relate mostly to frozen tissue and blood biospecimens. This is partly related to the drivers for creating research biobanks to meet demand specifically for this format of biospecimen. However more recently we and others have reported a significant shift in demand in favour of fresh[14] and fixed[12] biospecimens, especially those obtained from clinical archives, and also in favour of reuse of 'digital biospecimen data'.[43] For example the use of expression profile data available from online data repositories to explore relationships between gene expression and patient outcomes[55] or images downloaded for analysis by artificial intelligence approaches does not require analysis of new biospecimens.[56] These shifts in demand serve to reduce the need for large inventories and new biobank collections.

Many current biobanks face significant sustainability challenges.[50,57,58] Many inventories are dominated by frozen format biospecimens when relative demand for this format is declining[14] as noted above. The relevance of these inventories is also declining because their collections of biospecimens extend back several decades to when treatment approaches for the associated health conditions were often different.[54] Furthermore priorities across health research have also been changed by the COVID-19 pandemic.[59-64] We have previously highlighted the issue of changing demand for simple quality biospecimens, that make up much of the current inventories of tumour biobanks, versus complex quality biospecimens.[65,66] Hence many older biobanks may experience reduced demand for their inventories because they contain biospecimens or associated data that are no longer required by contemporary research.

Addressing the Balance Sheet

Given the preliminary conclusion that current supply in biospecimen inventories is well in excess of recent and projected demand, the issue of reducing the scale of inventories needs to be considered. As biobanks mature it is not unusual for them to need to discard some biospecimens in order to free up storage space or staff or financial resources dedicated to maintaining the biobank inventory. This can become necessary in order to take on new priorities and new biospecimens, as our analysis

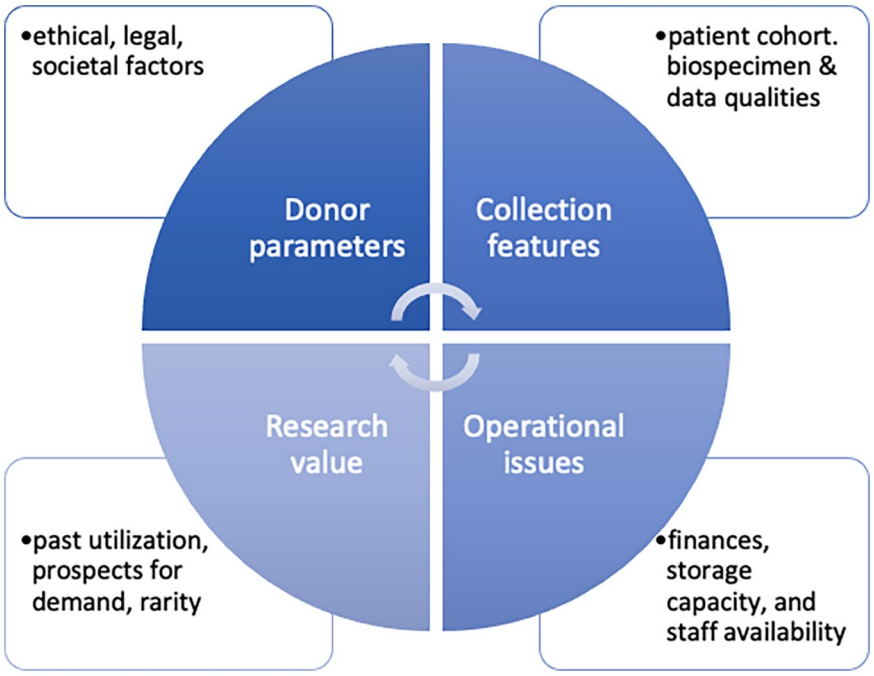

Figure 2. Four main aspects to the decision process to keep or discard collections of biospecimens. For many collections all aspects will be important to consider. Donor parameters include Ethical, Legal and Societal factors (eg, complex issues may arise due to specific conditions in the original donor consent form, or association with defined minority populations). Collection features include the characteristics of the patient cohort, the biospecimens, and the annotating data (high value features might include association of cohort with a specific new treatment, matching blood and tissue biospecimens collected at more than 1 timepoint, extended patient outcomes data). Operational issues include the availability of sufficient finances, storage space, and staff, to support ongoing maintenance costs. Research value indicators include rarity, extent of prior utilization, and assessment of prospects for future use.

above suggests. It can also become necessary because of major legacy events, such as reduced funding or limits to storage resources or biobank closure.[67,68] Nevertheless it is challenging to determine the best approach to rationalizing and culling biobank inventories.[69] Figure 2 summarizes the 4 main aspects to the decision process to keep or discard collections of biospecimens, and for many collections all aspects will be important to consider. Many classic operating model disease focused biobanks collect biospecimens using quality processes from generous patients. There is then an expectation from these donors that their donation will contribute to better treatment for others with the same disease.[70] There is also an expectation from the biobank that the value of each biospecimen will increase as outcomes data matures and that such biospecimens will eventually be used in valuable research.[54] This is particularly applicable to biospecimens that are judged to be rare and difficult to collect. However health research has finite resources and evolving priorities, and research needs change,[71-73] as has also recently been demonstrated by the COVID-19 pandemic.[59-63,74] Therefore, biobanks should regularly consider the value of the biospecimens in their inventories to prioritize portions of the inventory or the entire collection and accept that this evaluation becomes necessary with a major legacy event. In these circumstances biobanks should be prepared to discard low priority/high storage cost biospecimens in order to free up storage space and resources for higher priority/lower storage cost biospecimens.

Conclusions

This paper sets out to explore the issue of supply and demand for preserved biospecimens stored in academic health research biobanks that support biomarker research. It is based on relatively limited data available, but the estimates reached are consistent with the authors' personal experiences and observations in health research and with other sources that have addressed related questions. Although the precision of the numbers can be questioned and the deductions debated, the data clearly points to the conclusion that biospecimen supply exceeds current demand. Therefore, it may be important for individual biobanks to reassess the targets for their inventories[48,75] and shift resources towards providing prospective custom biobanking services.[3,76] In addition, where space and fiscal resources become restrictive, consideration of culling portions of inventories should also be considered.

Acknowledgements

P.W. gratefully acknowledges support for this work by the Biobanking and Biospecimen Research Services Program at BC Cancer (supported by the Provincial Health Services Authority), the Canadian Tissue Repository Network (funded by grants from the Institute of Cancer Research, Canadian Institutes of Health Research and the Terry Fox Research Institute, and from the Canadian Cancer Research Alliance). J.A.B. gratefully acknowledges previous grant support from the Cancer Institute NSW Biobanking Stakeholder Network for

the NSW Biobank Certification Program (Grant ID's 15/BIO/1-03 and 2017/BIO002) and support from the NSW Office of Health and Medical Research of the NSW Health Statewide Biobank.

Author Contributions

TT, JB and PW all equally contributed to the discussion that led to the genration of this manuscript. TT is the primary author. All authors have reviewed and discussed the results and contributed to the final manuscript.

Research Ethics Statement

No direct participation of human subjects was involved in this study and Research ethics board (REB/IRB) approval and informed consent are not required for this review.

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