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Review

Building a 'Repository of Science': The importance of integrating biobanks within molecular pathology programmes

Claire Lewis [a,*], Stephen McQuaid [a,b], Peter W. Hamilton [c], Manuel Salto-Tellez [a,b], Darragh McArt [c], Jacqueline A. James [a,b]

[a] *Molecular Pathology Programme, Centre for Cancer Research and Cell Biology, Queen's University, Belfast, BT9 7BL, United Kingdom*
[b] *Tissue Pathology, Belfast Health and Social Care Trust, Lisburn Road, Belfast, BT9 7AB, United Kingdom*
[c] *Bioimaging & Informatics, Centre for Cancer Research and Cell Biology, Queen's University, Belfast, BT9 7BL, United Kingdom*

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Abstract Repositories containing high quality human biospecimens linked with robust and relevant clinical and pathological information are required for the discovery and validation of biomarkers for disease diagnosis, progression and response to treatment. Current molecular based discovery projects using either low or high throughput technologies rely heavily on ready access to such sample collections. It is imperative that modern biobanks align with molecular diagnostic pathology practices not only to provide the type of samples needed for discovery projects but also to ensure requirements for ongoing sample collections and the future needs of researchers are adequately addressed. Biobanks within comprehensive molecular pathology programmes are perfectly positioned to offer more than just tumour derived biospecimens; for example, they have the ability to facilitate researchers gaining access to sample metadata such as digitised scans of tissue samples annotated prior to macrodissection for molecular diagnostics or pseudoanonymised clinical outcome data or research results retrieved from other users utilising the same or overlapping cohorts of samples. Furthermore, biobanks can work with molecular diagnostic laboratories to develop standardised methodologies for the acquisition and storage of samples required for new approaches to research such as 'liquid biopsies' which will ultimately feed into the test validations required in large prospective clinical studies in order to implement liquid biopsy approaches for routine clinical practice. We draw on our experience in Northern Ireland to discuss how this harmonised

* *Corresponding author.*
E-mail addresses: claire.lewis@qub.ac.uk (C. Lewis), s.mcquaid@qub.ac.uk (S. McQuaid), p.hamilton@qub.ac.uk (P.W. Hamilton), m.salto-tellez@qub.ac.uk (M. Salto-Tellez), d.mcart@qub.ac.uk (D. McArt), j.james@qub.ac.uk (J.A. James).

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approach of biobanks working synergistically with molecular pathology programmes is a key for the future success of precision medicine.

1. Introduction

Increased understanding of molecular and genetic mechanisms of disease has transformed treatment, prediction and diagnosis of cancer. Advances in proteomics and genomics such as mass spectrometry to simultaneously detect and characterise proteins and peptides, and next generation sequencing (NGS) for complete genome interrogation have had a profound shift in the ability of medicine to deliver on the promise of targeted therapies for patients with cancer [1,2]. Underpinning this shift is an increase in translational research activity which is heavily reliant on large numbers of high quality human biospecimens (tissues, blood and other bodily fluids) linked with reliable clinical and pathological data. In order to make such samples available for research, 'biobanking' has become the conduit for the standardised collection, storage and distribution of human samples, in turn, maximising biospecimen quality but also meeting many of the legal and ethical challenges for the use of human specimens in research [3]. Biobanks are now recognised as the cornerstone of biomarker discovery and personalised medicine [4]. However, in an environment where science is developing rapidly and where the conventional model for drug discovery and diagnostics is constantly challenged, it is important to explore how biobanks may be best integrated into existing operations for tissue based translational research.

Molecular pathology has emerged as an integrated discipline defining the relationship between genotype and phenotype, between basic molecular mechanisms and clinical applications and between bench and bedside, all factors at the core of a successful translational research programme [5]. Precision or stratified medicine is thus the application of predictive molecular pathology using conventional methodologies and/or high throughput analytical methods on human biospecimens to indicate the efficacy of a drug for an individual patient. With this article, we propose that biobanks are an integral part of a successful modern molecular pathology programme (Fig. 1) and are necessary to facilitate scientific discovery, advance research and meet the needs of the surrounding research community. Drawing on our experience in a Northern Ireland based biobank, we discuss how biobanking has synergy with other components of a molecular pathology programme, and how integration best creates a sustainable, affordable translational research infrastructure resulting in a repository not of samples but rather a repository of science.

2. Biobanks

2.1. Prospective and retrospective sample collection

Repositories containing high quality biospecimens linked with robust and relevant clinical and pathological information are required for the discovery and validation of biomarkers for disease diagnosis, progression and response to treatment. Ready access to such material is fundamental for meaningful translational research. In the case of cancer research, tumour banks have been established to procure fresh as well as formalin-fixed, paraffin-embedded (FFPE) tumour tissues and non-tumour control samples. These tissue collections are increasingly complemented by matched samples of blood, urine, saliva and other bodily fluids where appropriate. Despite a significant proportion of research in genomics and proteomics requiring the availability of fresh and/or fresh frozen tissues [6], recent studies have demonstrated comparable NGS results for both FFPE and fresh frozen tissue when fixed according

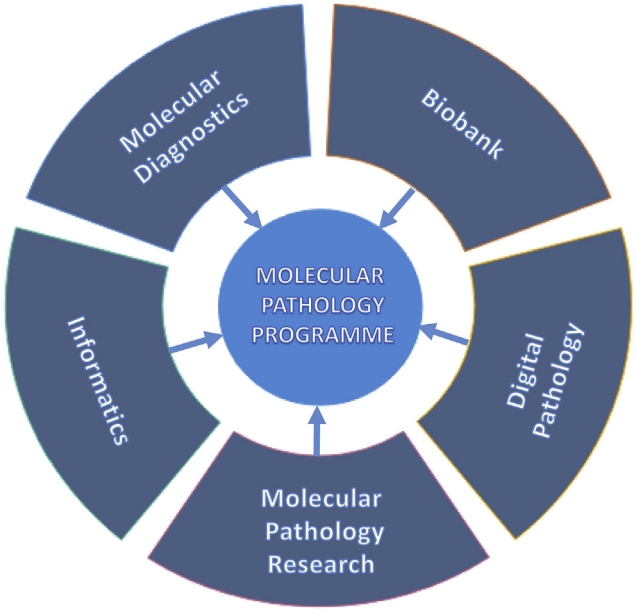

Fig. 1. Components of a comprehensive molecular pathology programme.

to a standardised protocol [7,8]. Whilst the authors caution that amplicon length needs to be taken into consideration when developing NGS gene panels for use with FFPE, it is expected that FFPE will become an increasingly attractive resource for high throughput platforms.

While prospectively targeted collections of appropriately consented human samples are the ideal for translational research programmes, realistically the systematic accumulation of large numbers of samples linked to clinical follow-up, apart from being costly, may take many years to become established. Yet readily available resources for translational research currently exist within many pathology laboratories; indeed, in the surgical pathology archives across the United Kingdom (UK)'s National Healthcare Service (NHS), vast numbers of FFPE tumour and non-tumour control samples are currently stored often untouched for a minimum of thirty years before disposal. There are contradictory opinions about the quality and quantity of nucleic acids that can be extracted from such collections of FFPE tissues and their potential use for downstream analysis [9,10]. In addition, tissues released from NHS archives are less likely to be linked with clinical follow-up data. However, these FFPE collections, when managed effectively, can provide an excellent resource to be interrogated for biomarker discovery and validation procedures. Innovative programmes can be established by biobanks to enhance their resources, in response to specific, scientifically valid and ethically approved requests from researchers, by engaging public hospitals to provide the biobank with access to defined cohorts of cancer tissues specifically for the creation of tissue microarrays (TMAs) and libraries of high quality nucleic acids extracted following standardised protocols. Such resources can be anonymised appropriately and made available in a timely manner for scientifically sound translational research activities. Biobanks which are able to facilitate use of NHS pathology archives are ideally positioned to support specific cancer subtype research, in particular rare tumours of unmet needs, collections which would otherwise take decades to accumulate prospectively.

2.2. Sample quality

The discovery and validation of new biomarkers (diagnostic, prognostic, therapeutic or pharmodynamic) is also becoming dependent on the modern well-standardised biobank. The regulatory and accreditation pathways that are required to establish a single biomarker as fit-for-purpose to progress through the many phases of development dictate that only tissue samples derived from biobanks with a high level of quality assurance should be able to be utilised in such testing [11]. In this context, the challenge for biobanking will be in the provision of the sample numbers that fulfil the required standards for testing. Samples may therefore be required from more than one biobank, and this will only be feasible if there is standardisation in the protocols for sample collection, processing and storage within a biobank network. The need for standardisation and harmonisation between biobanks in collecting, storing and providing tissue and clinical data for research was addressed in the UK by the National Cancer Research Institute's Confederation of Cancer Biobanks (CCB) who published accreditation standards for all aspects of 'Management' and 'Sample' quality in biobanking [12]. These standards also extended to biobank IT systems to facilitate interoperation and allow sharing of sample data at a national level [13]. More recently, the CCB has been tasked by the UK Tissue Coordination Centre to assist in the development of internationally recognised quality standards for biobanking in conjunction with Biobanking and BioMolecular resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC), a European wide infrastructure of biobanks and biomolecular resources [14].

2.3. Informatics

Biobanks require a dedicated mechanism for tracking samples in and out of the repository and for recording all stages of the sample journey from theatre, through pre-analytical processing steps, storage and ultimately to distribution for approved research projects. Ideally, this should be an electronic tracking system accessible by key participants in the custody chain and from different locations within the organisation including the ward, laboratory, office and biobank. This can be made convenient through the use of Web-based systems provided security and data integrity are maintained. However, the informatics capabilities of modern biobanks must also extend beyond just sample tracking and traceability [15]. Much of the success of a biobank will also depend on their ability to link samples to relevant and robust de-identified clinical, pathological and increasingly complex diagnostic molecular pathology information. This is critical as it allows researchers not only to further their understanding of tumour development and heterogeneity but also to track the course of the disease including response to specific treatment regimens and final clinical outcomes [16,17]. This mandates that modern biobanks have appropriate informatics in place which are capable of operating across different software interfaces [18]. The biobank informatics system should be seen as an 'integrated repository' of clinical and research information, facilitating collation of data sets from a variety of sources including clinical outcome data accessed through Cancer Registries, molecular test results (low and high throughput), data from national and international research programmes and hospital-based data sets all to form a single research IT platform.

Gone are the days however of collating information through simple documents and spreadsheets; in their place exist complicated hybrid database architectures attached to interrogative front-ends to facilitate the merger and interrogation of various data sets. An example of a successful biobank-integrative model is PICan, Pathology Integromics in Cancer, which marries this data capable biobank system to data analytics for researchers to warehouse information for data persistence and analyse in-situ [19]. The full capabilities of informatics synergistically leveraging biobank capabilities are beyond the scope of this review, and the authors would point to this perspective for added insight [20]. The current landscape of NGS that will allow data analytics from multiple modes (say RNA-seq: from gene fusions, single-nucleotide polymorphisms (SNPs) or differential expression) will require a dynamic architecture and strong database capabilities, perhaps even hybrid database models (MySQL, MongoDB and Neo4J). Established pipelines and controlled updates of annotations are important considerations to Biobanks where this information can also be archived on secure servers along with the raw files, such as fastq, that will allow data-mining in future studies. Access to such systems must be permission controlled with differentiating levels to allow researchers with the necessary approvals to see relevant information.

3. Molecular diagnostics

The assimilation of a molecular diagnostic service into research programmes with fully regulated biobanks is important for the following reasons:

3.1. Genotyping

Clinical reference laboratories in academic medical centres are beginning to generate abundant genotypic data from samples undergoing various formats of NGS for mutations such as *KRAS*, *EGFR* or *BRAF* [5,21]. This information is useful not only for the immediate management of the patient but also potentially for further discovery work on the same clinical sample in the future. In order to test for mutations in specific genes such as *KRAS*, *EGFR* or *BRAF* to direct treatments, molecular diagnostic laboratories routinely extract nucleic acids from FFPE tissues. Although molecular alterations can be detected at even low levels of tumour, many units providing molecular diagnostic services will require tumour samples to be sectioned, and a Haematoxylin and Eosin (H&E) slide annotated so that the technologist undertaking the test can enrich the percentage of malignant nuclei available for molecular analyses. An accurate description of tumour cellularity within the invasive component of the tumour on the tissue section should be viewed as paramount to the overall evaluation of the molecular test result [5].

Increasing use of high throughput technologies, such as NGS platforms for targeted sequencing of exon coding regions or a subset of 'genes of interest,' is an attractive proposition in both molecular research and molecular diagnostics [22] but will ultimately demand a greater ethical responsibility. Even with the use of targeted sequencing, there is a possibility that incidental findings (IF) of clinical significance may arise; while return of IF may be less fraught in the context of a clinical molecular test, there is a distinct lack of consensus about the management of IF in a research setting [23]. While debate about the ethical implications of NGS including consent and the ethical/moral obligation to return IF is outside the remit of this article, it is nonetheless important to acknowledge particularly in integrated molecular pathology programme where the boundary lines between research and diagnostics may be blurred [24].

3.2. 'Left-over' nucleic acid material

Increasingly so, molecular diagnostic laboratories are creating large collections of nucleic acids (both DNA and RNA) that are surplus to further clinical need following molecular testing. Such surplus samples if linked to clinical follow-up data, and the results of diagnostic and therapeutic testing could be placed directly into an integrated biobank for future research endeavours. In addition, the samples, coupled with the details of the annotation and the results of the molecular test, would remain available via the Biobank for validation of additional molecular diagnostic tests or service development programmes including those based on high throughput sequencing technologies [22]. The samples would also be available to those translational research programmes which require samples to be collected, processed and stored to the highest standards of external accreditation for both diagnostic laboratories and biobanks.

3.3. Quality

Translational and clinical molecular research needs to be performed in a 'laboratory quality framework' that will allow the transfer of such results into late stages of biomarker validation, clinical utility and licensing with little further downstream work. As a result, it is perceived that the processes of biobanking and translational molecular research are optimal when they are being undertaken in accredited laboratory environments.

4. Molecular pathology research

Molecular pathology research usually refers to two different but interconnected areas: research that can only be led by pathology investigators and research that requires a molecular pathology activity to be fully meaningful. The latter is self-explanatory: basic science

discoveries require validation of the clinical relevance in an accredited laboratory. This clinical confirmation needs to be undertaken by those who understand the clinical samples, who can interpret the necessary clinicopathological information (fundamental to understanding the clinical relevance) and who can establish sound correlations between biology, phenotype and genotype. This is all within the realm of the molecular pathologist. In reality, precision medicine has fundamentally evolved from the application of predictive molecular pathology using analytical methods on high quality human samples to indicate the efficacy of a drug for an individual patient.

There are research questions that can only be formulated from an in-depth knowledge of pathology. The archetype is the study of pre-neoplastic diseases. Only those that can recognise the phenotype of these tissue changes will be able to build the cohort of samples required to start the research process. As such, the possible interactions between pathology and other disciplines allow the development of novel interface areas such as 'pathology informatics' or 'molecular pathology epidemiology' [25,26]. Investigations of genes and gene products utilising well annotated, high quality samples from quality assured biobanks ensure a realistic, competitive time frame is created for the future development of novel diagnostics and therapeutic strategies in the overall goal of personalised medicine.

5. Digital pathology

Commercially available whole slide scanners can now rapidly generate high resolution digital images of entire tissue sections. This has a number of key advantages when integrated with biobanking and molecular pathology activities:

(i) *Searchable digital images and sample selection*: A digital image of the tissue can be recorded and stored as an integral part of the biobank information record for each tissue sample. This creates a permanent searchable image archive available for review at any time. Biobank applicants given access to the digital slide images can select specific cohorts from a group of images. Digital review readily facilitates the quality control and annotation of the pathology within individual cases and ensures researchers request the correct samples for their specific research project. Pathological review of the images can be carried out entirely on-line either locally or remotely using appropriate software, potentially removing the need to retrieve the glass slide for review by a pathologist [27].

(ii) *Digital sample annotation*: Digital pathology allows images to be digitally annotated and marked to highlight key tissue compartments and areas of interest. For example, the boundaries of tumour within a tissue sample can be digitally traced on the image and stored for future studies that might require macro- or micro-dissection of FFPE samples. Within biobanks, digital annotation of regions of interest during TMA design and construction can help to facilitate the assessment of biomarker expression in future experiments using the TMAs.

iii) *Remote biomarker scoring*: Digital pathology scans of research slides, including TMAs derived from biobanks break down many of the normal challenges associated with glass slides and provide flexibility and efficiency [28]. Novel tissue biomarkers can be rapidly viewed and scored on-line by pathologists or appropriately trained and competent scientists anywhere in the world, a key benefit for large multi-national, multi-site clinical trials or biomarker studies. Internet based access to digital pathology images can increase access to skilled pathologists for tissue review and biomarker evaluation even if they do not exist in one's own organisation.

It is important to note that stringent ethical and governance regulations still apply for the use of digital scan cohorts that are held within biobanks for research. Researchers must follow the same application processes to use stored scans for a specific purpose and then further amendments or new application is required if the scan sets are to be used for a secondary purpose. For example, a request for the use of archived biobank H&E scans to develop tumour cell recognition algorithms would need to fulfil the same ethical and governance requirements as a request for fresh H&E sections.

6. Convergence and synergy: advantages of a fully integrated molecular pathology programme

Advances in molecular diagnostics and the delivery of targeted cancer therapies require a dynamic partnership between academic researchers and pathologists or advanced practitioners with expertise in both tissue morphology and molecular pathology. A fully established molecular pathology programme, underpinned by a dedicated biobank, integrated with a digital pathology operation, offers a complete 'one stop' environment to facilitate research collaborations at a local level, bringing academic and clinical staff together within one hybrid laboratory. Such a unique hybrid environment consolidates manpower and equipment from healthcare and academia by amalgamating the technological capabilities of diagnostics and research.

The partnership which develops in a hybrid environment encourages increased research productivity and efficiency as it enables the transfer of skills and knowledge, allowing healthcare and academia to benefit from the other's expertise. This is illustrated in the example of biomarker science, where association between the two organisations is considered essential to biomarker

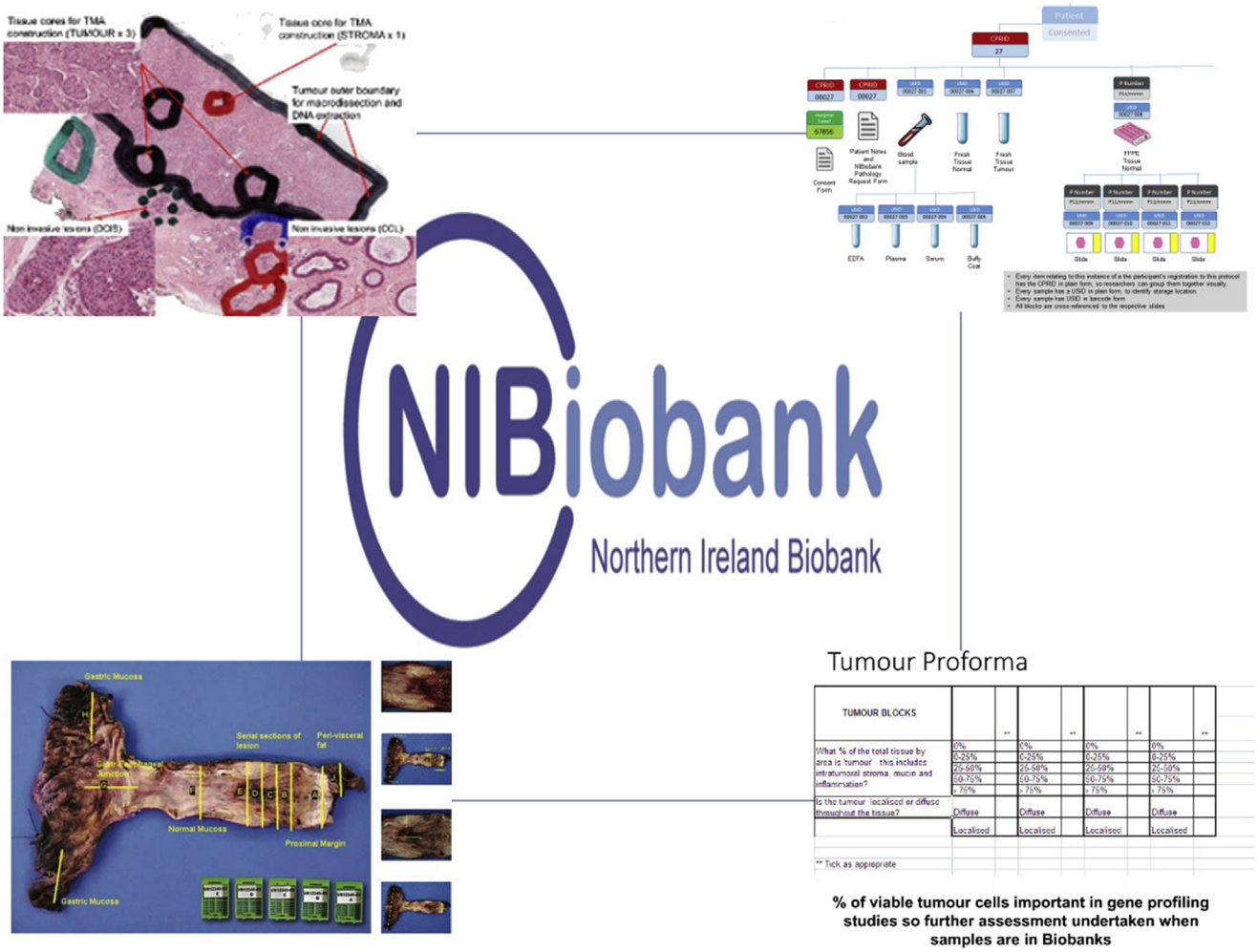

Fig. 2. Key components of a cancer biobank: clear workflow of sample collection with unique identifier for each sample derivative linked to the consented patient; macropath images to record sites of representative tumour or normal tissue blocks; tumour proforma to record % of tumour and nature; digital images of annotated H&E with descriptions of regions of interest of cores for tissue microarrays (TMAs) or for nucleic extractions.

discovery and validation [29]. Collaboration enables researchers involved in biomarker science and clinicians involved in tissue procurement to collectively develop protocols and procedures which support acquisition of high quality, well defined biospecimens for use in biomarker research.

It is widely documented that biobanks face significant challenges in terms of funding and resources to ensure long-term sustainability [30,31]. Similarly, healthcare and academic institutions are currently facing unprecedented budget constraints and financial challenges. The creation of hybrid facilities presents a unique opportunity to overcome some of the mutual challenges faced by healthcare and academia organisations to avoid duplication of effort [32]. Partnerships allow for shared use of laboratory equipment for tissue processing, tissue embedding, H&E staining and so forth, thus improving efficiency and lowering costs within both organisations. Integration of biobanking activities within a hybrid molecular pathology programme encourages the development of biomedical and clinical scientists with both clinical diagnostic and research expertise. This convergence of skills and knowledge facilitates rapid transfer between molecular diagnostics in the clinical setting with scientific pursuits in the academic setting and vice versa. Integrated molecular pathology programmes facilitate strong collaborations between academia, regulatory authorities and pharma.

It is also important to highlight the increasing importance in liquid biopsies, based on academic research developments and the need to develop minimally-invasive diagnostics [33–35]. Such liquid biopsies are reflective of the *in vivo* situation in the patient as opposed to a 'segment' of the tumour; as such, they may allow for longitudinal analyses of patient responses to therapies without the need for costly, painful invasive

procedures. Progressive solid tumour biobanks, working in close collaboration with molecular pathology programmes, are ideally situated to develop and standardise the pre-analytical methodologies required for acquisition of quality assured liquid biopsy samples for the validation of tests on circulating biomarkers (i.e. circulating free DNA, microRNAs, exosomes or microvesicles, circulating tumour cells) from many tumour types.

7. The Northern Ireland model

All the considerations for a modern, integrated and synergistic molecular pathology programme have been taken into account when designing the Northern Ireland Molecular Pathology Laboratory. A key element of this programme is the integration of a biobank with the primary aim of moving beyond the classic collection of biological samples and associated clinical information, to become a true repository that involved the scientific results generated by the different collaborators and users. The Northern Ireland Biobank (NIB) has full ethical approval for the collection, storage and distribution of tumour and non-tumour control tissue and associated bio-samples to support translational research programmes regionally and beyond. Key components of the NIB model such as unique identifiers for samples linked to the consented patient, tissue proformas completed by consultant histopathologists and archives of digital images (macroscopic and microscopic) are outlined in Fig. 2.

Established as a joint venture between Queen's University Belfast and the Belfast Health and Social Care Trust (BHSCT), the NIB has become fully integrated into the newly restructured molecular pathology programme within the University's designated cancer research facility, the Centre for Cancer Research and Cell Biology. This new molecular pathology department has been purposely designed in partnership with the BHSCT pathology laboratories to create a hybrid diagnostic and translational research operation, underpinned by the NIB. As well as integration within a molecular pathology programme, the NIB has distinct advantages including:

- Ethical approval for the prospective collection, storage and distribution of cancer tissues and related biospecimens to researchers
- Ethical approval to access tissue samples in the BHSCT pathology surgical archives including surplus DNA or RNA from molecular diagnostics
- Established relationships with the clinical care teams and the Northern Ireland Cancer Registry for the acquisition of de-identified clinical and pathological information associated with NIB samples
- A secure information management system which incorporates digital imaging of NIB tissue samples
- Facility for analysis of tissue microarrays—a TMA Toolbox

8. Challenges for the future

The fully integrated molecular pathology programme of which the NIB is an integral component offers a complete end to end molecular diagnostic and translational research operation. This co-operative effort of biobanking, molecular diagnostics, translational research and digital pathology has the potential to deliver real improvements in the clinical management of cancer. The rapidly changing face of sample requirements for molecular diagnostics, emerging technologies or for new research paradigms, for example, cfDNA or circulating tumour cells require biobanks to continuously review and adapt their own collection protocols. The NIB which is fully integrated within a diagnostic and research molecular pathology environment is ideally suited to promptly create and quality control these new sample collections to provide the high quality sample collection for clinical validations or researchers.

Furthermore and moving forward, there is a need to exploit the collective resources of biobanks and harness the knowledge generated from individual molecular pathology programmes to continue to drive and improve cancer diagnostics and research. Work has already begun in Europe and North America to address the practicalities of integrating biobanks into larger networks with shared informatics [36]. However, many legal and ethical challenges still exist to such integration.

9. Summary

It is our opinion that modern research will need to be driven by key new paradigms: clinical utility, long-term affordability and high-end integration. The consequence of this is clear: we need a new paradigm for the integration of molecular diagnostics, biomarker validation and biomarker discovery. This integrated paradigm must be led by molecular pathology programmes with biobanking as a critical component of the overall process (Box 1).

Box 1. What defines a high quality formalin-fixed, paraffin-embedded (FFPE) tumour tissue sample?

- Full clinical details
- Full pathology report availability
- Cold ischaemia time
- Fixation type and time
- Processing and storage history
- Full pathological annotation:
  - % tumour
  - % normal
  - % necrosis
- Availability of quality assurance data
- Matching normal samples available
- Searchable H&E scan availability

Conflict of interest statement

Authors declare no conflict of interest.

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