Chapter 8

Laboratory/Pathology Services and Blood Bank

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Comprehensive cancer care (CCC) brings together clinical services, research and education for the benefit of cancer patients. The main input of laboratories and pathology services to CCC service is rapid access to high-quality diagnostics, which will be much of the focus of this chapter. In addition, the support of laboratories toward education, research and development is also essential to attain the status of world-class CCC, and this is reflected in the definition given by the National Cancer Institute [1].

Pivotal to all high-quality cancer care is the ability to achieve accurate and detailed diagnosis so as to enable prognostication and treatment strategies. This has increasingly moved from morphological and descriptive diagnostic techniques to a molecular landscape where tumour genomes are interrogated for their tumour signatures. All of this sits within the purview of pathology and its laboratories.

The other essential role played by the laboratory/pathology services is the support of patients undergoing treatment and follow-up: delivery of safe blood, a stem cell processing lab, rapid analysis of blood samples, identification of infectious agents amongst a host of other functions.

World-leading CCC centres are not only international reference centres for patient care, their genomics research and access to large volume clinical material and data aim to embed personalised medicine as part of patient care, likely in investigational clinical trials [2–4]. The ability of laboratory and pathology services to

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obtain, analyse and integrate ever-increasing amounts of complex information helps the modern cancer multidisciplinary team (MDT) to achieve this goal.

We have subdivided this chapter into the broad headings of what we consider to be the fundamental roles of pathology and laboratory service in the CCC as follows:

1. Laboratory and pathology support for screening programs and arriving at a cancer diagnosis
2. Laboratory and pathology support for maintaining quality supportive care throughout cancer treatment
3. Specific pathology support for running stem cell transplant/cellular therapy programs and pathology support for running cancer clinical trials and research.

Relevant to all aspects of laboratory and pathology services in CCC is the requirement for *accreditation* or *external review* and control. Accreditation is public recognition by a healthcare body of the achievement of standards by a healthcare organization, demonstrated through an independent external peer assessment of that organization's level of performance in relation to the standards. Accreditation standards may be regional or national, or they may be international and aim to define quality standards and achieve uniformity in a health system [5]. Whatever laboratory or pathology service you provide, this process is being used worldwide to ensure that results from labs are comparable, clinically useful and safe.

A CCC centre would be expected to drive the development of local, national or international evidence-based guidelines in an area of cancer care. The ability of a CCC centre's laboratory and pathology service to access high-quality data, with high throughput of patient cases and samples would be best suited to this function. This is reflected in major world CCC centres' laboratory involvement in national and international guidelines seen today, for example,

- Comprehensive Cancer Center Ulm, Ulm, Germany – input into European Society of Medical Oncology (ESMO) guidelines in chronic myeloid leukaemia, chronic lymphocytic leukaemia and acute myeloid leukaemia [6–8].
- INCLIVA, University of Valencia, Spain – input into several ESMO guidelines including metastatic colorectal cancer, anal cancer, hereditary GI cancers, hepatocellular cancer [9–12].
- Dana-Farber Cancer Institute, Boston, MA, US – into ESMO guidelines for advanced breast cancer, but also many American Society of Clinical Oncology guidelines [13, 14].

Information management, maintaining of databases and storage of laboratory/pathology data, as well as management of laboratory research data are also major considerations but will be not covered in this chapter. Most CCC centres have invested heavily and developed systems capable of dealing with vast data quantities.

Laboratory and Pathology Support for Screening Programs and Arriving at a Cancer Diagnosis

The input of laboratory/pathology services into the modern cancer MDT or “tumour board” contributes to the formation of a full “integrated” cancer diagnostic report. An integrated report at its most basic, from a lab/path perspective, needs cellular pathology and histopathology. However, CCC centres add immunohistochemistry, cytogenetics, molecular, genomic analysis and immunophenotyping (particularly in haemato-oncology) as key components of the integrated report, given that many diagnoses will not be complete or therapeutic options will not be fully explored without these techniques [15].

An MDT or “tumour board” will need to integrate all of the above information with clinical and radiological data, and it is in part the responsibility of laboratory and pathology services to achieve this. It is crucially this “integration” process that is the hallmark of CCC, and then “translating” the integrated report into excellent care and facilitating patient-centred research. Support and personal attendance of senior scientists, laboratory staff and pathologists is increasingly vital to the modern cancer MDT.

In addition to individual patient care, population-based cancer screening programs that may be linked to CCC centres will also depend on laboratory and pathology support from cervical pap smear cytology to faecal occult testing to supporting research-based programs like UK-based 100,000 Genomes Project [16].

Cellular pathology and histopathology will require the capability for specimen fixation, embedding into paraffin, tissue slicing, and staining. The pathologists reporting of samples at CCC centres will frequently require subspecialty expertise or access to such expertise via international networks, especially for rare cancers. In many cases, this is facilitated by telepathology which may include sharing of selected static images, whole-slide scanning, dynamic non-robotic telemicroscopy, and dynamic robotic tele-microscopy. Selected static image sharing can be as simple as a microscope, digital camera, and Internet connection and has been successfully used in Butaro Cancer Center of Excellence in Rwanda, where a static-image telepathology system was established after a training period for field selection, in collaboration with the Dana-Farber/Brigham and Women’s Cancer Center [17, 18].

Immunohistochemistry (IHC) now provides important diagnostic and prognostic information as well as guiding therapeutic options for cancer care. IHC, the application of antibody stains with a chromogenic or fluorescent readout to identify tumour markers, their quantity and location and interpretation of significance is nowadays ubiquitous. An important choice to be made is whether to carry out IHC on formalin-fixed, paraffin-embedded samples or on fresh frozen samples. Paraffin embedding offers superior tissue/cell morphology, but antigenicity is potentially compromised by the fixation required for paraffin-embedded samples. A CCC would require

access to facilities capable of freezing samples, storing samples and access to many antibody panels that often need refrigerated storage themselves [19, 20].

Cytogenetic studies, the study of chromosomal structure, or karyotyping was first utilised in cancer diagnostics in the 1960s with the discovery of the Philadelphia chromosome. Classical karyotyping or banding techniques (G-, Q-, R- banding) nowadays is a limited, but useful genome-wide screening tool. However, it requires a high mitotic index of cells, good chromosomal morphology and is time-consuming. The drive for rapid results and the ability to analyse preserved samples in interphase has pushed molecular cytogenetic techniques such as fluorescence in situ hybridisation (FISH), multicolour-FISH (M-FISH and SKY) and competitive genome hybridization (CGH) into the forefront of modern cancer diagnostics. The ability of the CCC centre to bridge basic research to clinical practice using these techniques has expanded rapidly in recent years. Access to reliable and specific marker probes and increasingly automated methods would help to facilitate expansion of testing capabilities in what has traditionally been a highly labour-intensive technique.

Molecular cytogenetic analysis is particularly useful in haematological and soft tissue tumours albeit historically less used in solid tumours due to a scarcity of specific associated cytogenetic abnormalities and difficulty in processing the sample for analysis. As more and more targetable tumour markers are identified, FISH studies are increasingly useful to identify upfront whether patients can be offered targeted treatment. Some examples of solid tumour FISH use are: differential diagnosis between teratoid/rhabdoid and medulloblastoma/primitive neuroectodermal tumours and dual colour FISH for HER-2 in breast cancer as a prognostic marker and predictor or therapy response [21].

Genetic analysis of tumour and patient DNA in modern cancer care has been revolutionized with the recent advances of next-generation sequencing (NGS), hybridization capture targeted multigene panels and computational data analysis [22]. Discussing the various genome analysis techniques, their implementation and practical aspects are beyond the scope of this chapter; however, there are important principles to consider. Technical challenges related to the quantity and quality of tumour sample will have a direct impact on your ability to use genetic studies related to your laboratory's knowledge and equipment. Sample preparation methodologies are crucial to maximising the chance of obtaining useful information from what may be a small, poor quality and formalin-fixed biopsy sample.

Most centres now run tumour-specific multi-gene panels which are “trade-off” between slow turnaround, labour-intensive genome-wide screening approaches and potentially low-yield single mutation screening with Sanger sequencing. A myeloid gene panel for suspected Acute Myeloid Leukaemia, for example, could contain >20 genes which are of high specificity and sensitivity for the disease and may directly alter prognosis and treatment options, for example, IDH mutations [23]. The decision as to the depth, breadth and methodology used in multi-gene panels will be very much centre-dependent, taking into consideration the throughput, turnaround time, equipment, cost and skill set of your centre. Hereditary cancer

syndromes are a field of CCC that has greatly benefited from massively parallel sequencing, as most known familial cancer syndromes are represented by several distinct genes that may cause similar clinical manifestation. The ability to scrutinize many known or potential disease-causing mutations is very powerful [22]. For instance, in Lynch syndrome or Hereditary non-polyposis colorectal cancer – a screen might involve NGS to identify MLH1, MSH2, MSH6, PMS2, or EPCAM mutations, then PCR-based microsatellite instability testing [24].

The post-genomic era has created vast quantities of data for CCC, which in most centres has spawned a “cancer genomics MDT”, a genomics review board (as in the UK) or “molecular tumour board” (as in US institutions like Brigham and Women’s Hospital) [25, 26]. The genetic complexity of cancer, the relevance of mutational changes and the application of multiple NGS-based assays create a challenge in the interpretation and clinical application of this data. Increasingly, this makes it necessary for pathologists and molecular scientists to be core and essential members of the multidisciplinary team in deliberating the final clinical recommendation based on multiple complex test results [27, 28].

Other molecular studies for diagnosis and disease monitoring, such as tumour markers, immunological studies such as protein electrophoresis and high-performance liquid chromatography (HPLC) are discussed in the section “Laboratory and Pathology support for maintaining quality supportive cancer care”.

Immunophenotyping using flow cytometry (FCM) is extensively used in haematology but can also be ancillary to the diagnosis of metastatic adenocarcinoma and malignant mesothelioma in effusions. The limitations in haematological cell morphological analysis are vastly compensated for by this technique; it can be performed in a matter of hours and provides key information for the diagnosis, classification and monitoring of many haematological malignancies. Single-cell suspensions of solid tumours and circulating tumour cells are being used and are likely to be of increasing clinical use as more research is developed. Panels of FCM markers are also used in the assessment of neuroblastomas, primitive neuroectodermal tumours, Wilms’ tumour, rhabdomyosarcomas and germ cell tumours [29]. FCM can not only provide analytic data, but also be used as a cell sorting method to enrich cell populations for genetic studies. With the use of multi-colour FCM, laboratory scientists and clinicians will both need to have an understanding of the diagnostic relevance and interpretation of results. It is of key importance that clinician and scientist are sharing information.

It is also important to mention that, although we have discussed cytogenetic, genetic and immunophenotypic analyses in the “diagnosis” section, all are of immense value in disease monitoring and monitoring of treatment response. With the concept of minimal/measurable residual disease (MRD) and the emerging knowledge that tumour genetic evolution can influence relapse and treatment failure risk, there is an increasing challenge to pathologists, geneticists and laboratory services to standardise procedures, increase testing capacity and engage with clinicians throughout the patient’s treatment.

Laboratory and Pathology Support for Maintaining Quality Supportive Cancer Care

Microbiological services are essential in a CCC centre, as immunocompromised patients undergoing chemotherapy/immunotherapy often are highly vulnerable to infection. This includes suspected infections that may be rare or atypical, antimicrobial resistance monitoring, monitoring of therapeutic drug levels (e.g. gentamicin, vancomycin, voriconazole, ganciclovir) and translating microbiological research results into practice in cancer patients.

Prevention of infectious disease, such as screening of blood-borne virus exposure prior to chemotherapy, will require serological study facilities, screening for Healthcare Associated Infections (HAI) potential, for example, MSRA and swabbing may also be required in large healthcare facilities. The treatment of infectious disease during chemotherapy will require the capability for blood and fluid bacterial and mycological culture, viral PCR capabilities (e.g. respiratory virus swab PCR) and senior microbiology input to interpret results and advise on therapy options.

Biochemistry and haematology laboratory services with capabilities specific to cancer care are vital in CCC. Coagulation studies, automated cell counting technology and manual differential cell counting in blood and marrow samples, provided in haematology laboratory services are both diagnostic in their own capacity (for haematological malignancy and bone marrow infiltration of other solid tumours) as well as supportive for all aspects of CCC. They allow monitoring myelosuppression during chemotherapy/radiotherapy, monitoring response to infectious disease, determining safety for cancer-related procedures (e.g. coagulation assays prior to surgical resection), as well as the facility to deal with complex problems of haemostasis in cancer patients (e.g. complex venous thrombo-embolism, anti-Xa monitoring, acquired haemophilia, etc).

Biochemistry support for CCC at its core entails electrolyte monitoring, surrogates for organ function or damage, for example, U&E, LFTs, BNP, protein-based and immunological assays for disease monitoring used in solid and liquid tumours, for example, prostate-specific antigen (PSA), cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA) and serum protein electrophoresis, serum free light chain analysis and HPLC (the latter specifically for diagnosis of pheochromocytoma, neuroblastoma and carcinoid syndrome) [30, 31].

Blood bank and transfusion support: This includes the acquisition, storage and appropriate use of blood products. The laboratory infrastructure required for the storage of blood products and the information technology support used in electronic cross-matching, product storage tracking and monitoring fridge performance is considerable, but necessary in large cancer centres particularly in those specializing in haemato-oncology. Laboratory support needs to be provided to clinicians to guide the appropriate use of blood products and to provide appropriate protocols for emergency situations, such as massive haemorrhage. Laboratory support is required for the detection of complex auto-, allo- and drug-induced antibody presentations in the multiply transfused or treated patient (e.g. Daratumumab) and management/

investigation of transfusion reactions or product refractoriness. Access to irradiated blood products is crucial for many cancer patients for prevention of transfusion-associated Graft vs Host Disease as well as access to HLA/HPA-matched products in platelet refractory cases.

Pathology Support for Running Stem Cell Transplant/ Cellular Therapies

Haematopoietic stem cell transplantation (HSCT) and cellular therapies (CAR-T) require many unique laboratory facilities. Broadly, we have subdivided these into:

1. Biochemistry, microbiology and histopathology services
  2. Histocompatibility and immunogenetics (H&I)
  3. Apheresis and cell management
  4. Chimerism studies
1. Monitoring of drug levels specific to stem cell transplantation monitoring such as ciclosporin and tacrolimus. Due to the highly immunosuppressive nature of stem cell transplantation, more intensive microbiological screening and monitoring is required, such as regular CMV, EBV, and adenovirus viraemia screening (preferably by PCR testing), pre-transplant serology HIV, HTLV, viral hepatitis, syphilis, toxoplasmosis and other mandatory tests for communicable diseases. Histopathologists with expertise in identifying graft-versus-host disease (GvHD) from biopsy samples are required to support a haematopoietic stem cell transplant service. HSCT and CAR-T centres must have a 24-hour on-site blood bank, haematology and biochemistry laboratory services and access to stem cell collection and processing facilities.
  2. Apheresis is the most commonly used technique for stem cell collection requiring staff with both clinical and laboratory training in the use of this procedure. CCCs will need access to facilities for storage and cryopreservation of haematopoietic cells from a variety of sources. Close coordination with apheresis units is required to ensure adequate CD34+ cell doses from stem cell collections. Furthermore, HSCT centres require the preparation of T cell therapeutic (TC-T) aliquots (formerly called donor lymphocytes infusions or DLI) in measured CD3 doses. Quality assurance methodologies by validated procedures will be necessary such as the use of microbiological tests to assure the suitability of donors and the safety of products. The use of flow-cytometric and/or tissue culture assay systems to demonstrate progenitor viability and process suitability is mandatory [32–34].
  3. Histocompatibility & Immunogenetics (H&I) services in support of cancer care are mostly involved with HLA typing and antibody screening which is mandatory for all allogeneic transplant centres. However, H&I is also important for other ancillary services with respect to cancer such as screening for

heparin-induced thrombocytopenia, HLA-polymorphism testing (for lapatinib-induced DILI in breast cancer) and the diagnosis of platelets refractoriness (using PIFT and MAIPA studies). In recent years, accredited H&I laboratory facilities perform timely DNA-based intermediate and high-resolution HLA typing via a form of sequence specific priming, or NGS. The H&I lab will allow clinician access to bone marrow registries to facilitate access to matched unrelated donors and cord blood registries [32, 35].

4. Recent advances and understanding in cellular immunotherapy as a major therapeutic pillar in cancer treatment, especially, haemato-oncology has increased the reliance on and interdependency of the stem cell processing laboratory and more advanced Good Manufacturing Practices (cGMP) cell therapy facilities, often under the management of pathology. This will require expert staff individuals trained in the manufacture of complex cell therapy therapeutic products [35]. The area of chimeric antigen receptor T-cell therapy (CAR-T) is an example of this with numerous worldwide clinical trials and with the cell therapy laboratory requiring access to apheresis, bespoke CAR-T manufacture requiring viral vectors, genetic modification, packaging, systems for T cell expansion and vapour liquid phase nitrogen storage [44].

Pathology Support for Running Cancer Clinical Trials and Research

Laboratories and pathology services are integral to the running of clinical trials and biomedical cancer research. Development and discovery of genetic/biomarkers of disease (or disease classification and prognostic stratification), drug development, nanotechnology, cellular therapy development, gene therapy are a few broad examples. Education and training of academics, clinicians and laboratory staff is at the forefront of comprehensive cancer care, and this includes both standard-of-care clinical practice and investigational clinical trials supported by ethical guidance at national and international level (e.g. FDA Good Laboratory practice (US), EU clinical trials, Good Clinical Practice, the Declaration of Helsinki and the Human Tissue Act (UK)) [36].

From a laboratory perspective, apart from the above-mentioned facilities (high-quality diagnostic techniques, monitoring of biochemistry and haematology lab support), clinical drug trials may need the facilities to synthesize and purify new compounds, assess drug pharmacokinetics and pharmacodynamics in cell, animal or human subject samples. Laboratory involvement can be from drug discovery and development right through to post-market safety monitoring.

Biobanks, with respect to cancer care, are the storage of large numbers of biological samples for use in research – ranging from tumour tissue samples, genetic material and drug levels or biomarkers from serum, saliva, stool, etc. Biobanks are

often utilized by major CCC research centres, giving research teams rapid access to vast quantities of samples spanning a long time period [37–40]. Although biobanks are often disease-oriented, for example lung cancer, they may be population-based to determine susceptibility of disease development.

Laboratory support in biobanking will require secure, well-maintained, long-term cryogenic storage facilities (with temperature control documentation and backup systems in case of power failure), and sample tracking capabilities. Traceability is critical and the strict adherence to protocols ensuring appropriate patient informed consent. Standard operating procedures for laboratory sample handling and processing are also highly desirable for reproducibility and data reliability. Such biobanking facilities are often required to comply with stringent operating policies and meticulous laboratory support in order to gain a human tissue act license [41]. To this end, many international groups have written “best practice guidelines” for example, International Society for Biological and Environmental Repositories (ISBER) and NCI Best Practices for Biospecimen Resources. They have also tried to address the ethical concerns that often surround biobanks such as ownership of specimens and the extent as to which specimen donor can consent to all forms of future research [42, 43].

In conclusion, pathology and its laboratories are central in supporting every facet of cancer care in a CCC center, from diagnosis, biobanking, patient support during treatment, research, therapeutic drug manufacture and development. The ability to support all of this will always need to be balanced against time and costs. As such, any strategic planning for the setting up of a CCC center should allow for careful deliberation and meticulous planning on the scope and breadth of pathology services to be set up.

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