GUIDE FOR ESTABLISHING A PATHOLOGY LABORATORY

in the context of cancer control

World Health Organization

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FOREWORD

MANY DEATHS FROM CANCERS CAN BE PREVENTED WITH APPROPRIATE, TIMELY DIAGNOSIS AND EFFECTIVE TREATMENT.

In 2017, the global resolution WHA70.12 on Cancer prevention and control in the context of an integrated approach called upon World Health Organization (WHO) to improve access to cancer prevention, diagnosis, treatment and palliative care for children and adults. In the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020, screening and multimodal treatment of early stage cervical, breast, colorectal cancers are also listed as effective and cost-effective interventions in low- and middle-income countries.

These interventions, however, are applicable only when pathology services are in place, because without the identification of malignant nature of the disease and determination of histopathologic features, effective treatment cannot be delivered. Expansion of national cancer control programmes, therefore, inevitably requires strong and reliable pathology services. Countries with limited pathology service capacity may need to establish a new pathology laboratory or strengthen the existing laboratory function, ensuring safety and quality.

This guide is intended to support programme managers and health officials to understand the minimum requirements for establishing a pathology laboratory with histopathology and cytopathology services. As there is no single approach that fits all situations, the implementation of the elements of this guide will vary depending on the local context and need to be adapted accordingly.

The cancer burden is rising globally and there are still too many deaths from cancers that can be prevented with appropriate, timely diagnosis and effective treatment. Improving access to essential pathology services is a critical step for improvement. It is also of paramount relevance to achieve universal health coverage, framed within the United Nations Sustainable Development Goals (SDG) agenda for health, through an integrated, cross-sectoral and multidisciplinary approach across the continuum of care. Heath systems that are tasked with achieving SDG must improve access to essential pathology services.

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ABBREVIATIONS AND ACRONYMS

EQA	external quality assessment
gm	gram
H&E	haematoxylin and eosin
IHC	immunohistochemistry
ml	millilitre
NBF	neutral buffered formalin
PPE	personal protective equipment
SOP	standard operating procedure
WHO	World Health Organization

SECTION 1

INTRODUCTION

1.1 GLOBAL BURDEN OF CANCER AND THE ROLE OF PATHOLOGY

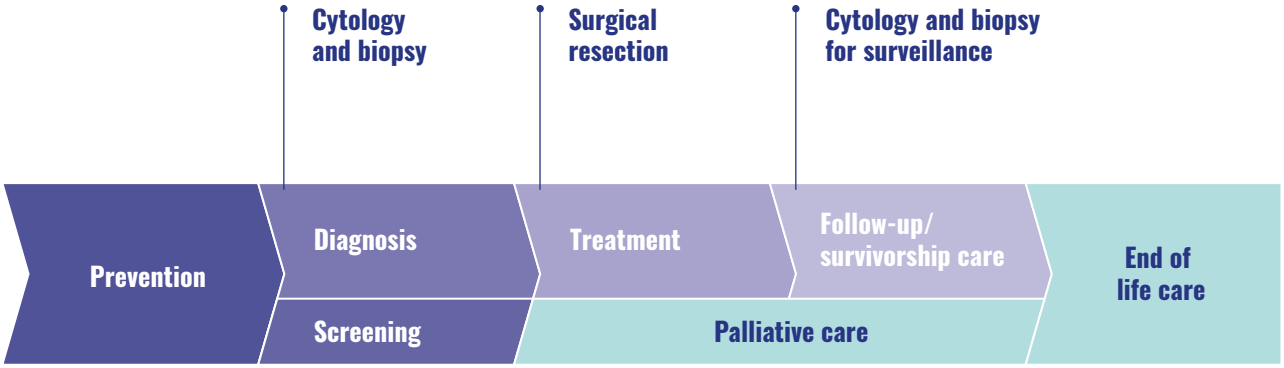
Cancer is a group of malignant neoplasms that can affect any part of the body. It is the second leading cause of mortality globally with an estimated 18 million new cases and 10 million deaths every year (1). Cancer incidence is rapidly rising in all countries, and projected to increase to 30 million by 2040 (2). The ability to provide screening, early diagnosis, treatment and follow-up has a huge impact on care and patient survival.

FROM **18 MILLION** NEW CANCER CASES IN **2018**

TO **30 MILLION** BY **2040**

Pathology services are required for multiple purposes in cancer control (Figure 1). First, the definitive diagnosis of cancer must be made by morphological and phenotypical examination of suspected fluids or tissue. For solid tumours, optimal treatment of cancer also depends on various histopathologic parameters, including the type, grade and extent of cancer. Cytopathology is commonly used for screening, diagnosis and surveillance of certain cancers.

FIGURE 1. COMPONENTS OF CANCER CONTROL AND THE ROLE OF PATHOLOGY



Source: Adapted from WHO 2017 (3).

WHAT IS PATHOLOGY?

Pathology and laboratory medicine (PALM) is a complex set of medical sub-disciplines covering a wide range of diagnostic testing that is needed to deliver treatment and care for many diseases (Figure 2) (4). It is estimated that 70% of all medical decisions are made based on laboratory diagnoses (5). PALM is of central importance in making a diagnosis, guiding treatment, informing prognosis and monitoring outcomes for an individual to maintain their well-being. It also contributes to public health surveillance and disease registries (4).

AN ESTIMATED

70%

OF ALL MEDICAL DECISIONS ARE MADE BASED ON LABORATORY DIAGNOSES

FIGURE 2. ORGANIZATION AND INTEGRATED STRUCTURE OF PATHOLOGY AND LABORATORY MEDICINE (PALM)

Source: Adapted from Wilson et al. (4)

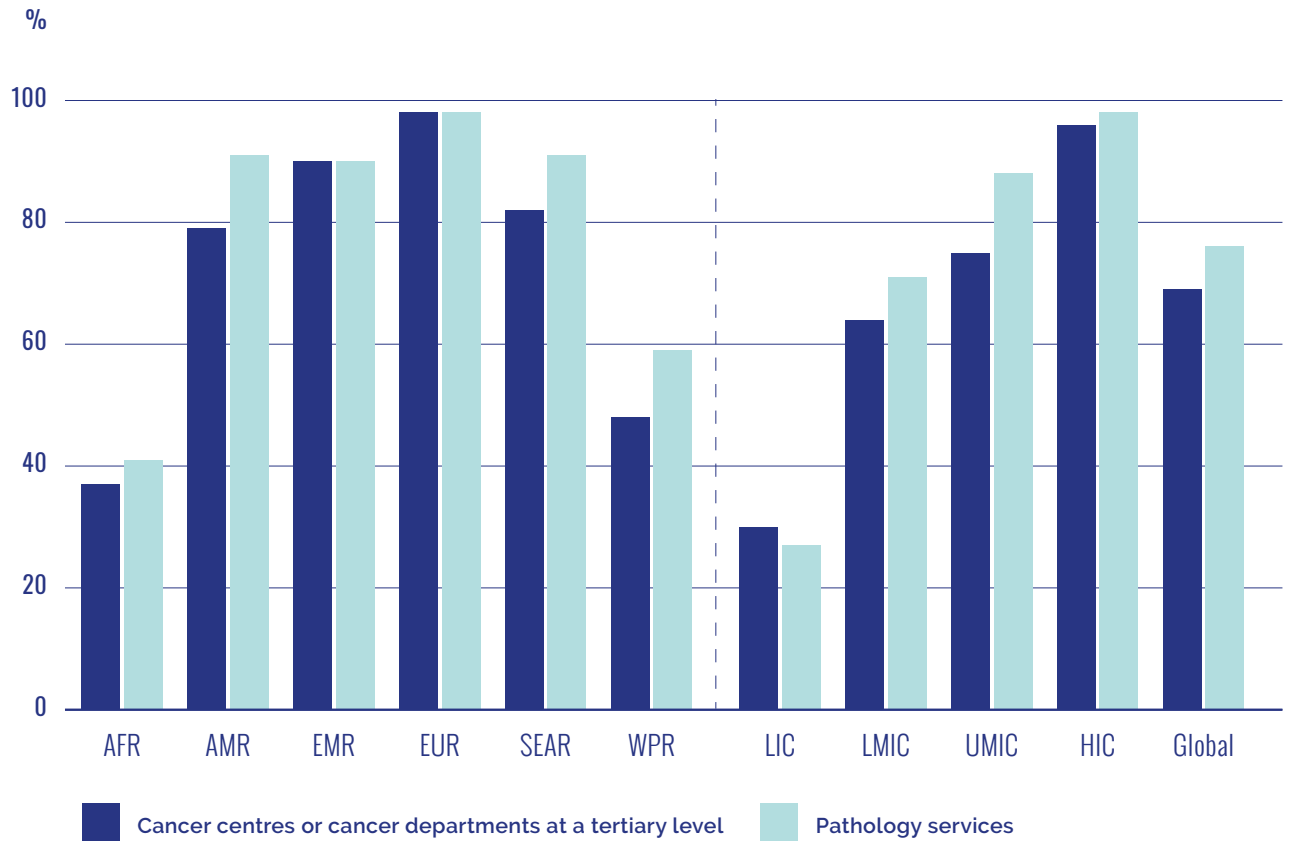
The term "pathology" as applicable for the name of medical discipline can be used differently by country and setting. For example, it could refer only to histopathology and cytopathology, include forensic pathology, or cover all or more sub-disciplines described in figure 2. To avoid confusion, the term "pathology" in this document mainly refers to histopathology and cytopathology, which examine morphological changes of tissue and cellular structure caused by a disease.

Pathology services are not only critical for management of cancer, but also support diagnosis of other diseases, including infection, inflammatory and degenerative disorders.

1.2 CHALLENGES IN ACCESS TO PATHOLOGY

Despite its critical importance to cancer management, there is a significant gap in access to pathology services around the world. Figure 3 compares the availability of pathology services by WHO region and World Bank income group (6). While 95% of high-income countries report pathology services being generally available in the country (defined as being accessible in 50% or more of public health-care facilities), only 26% of low-income countries did so.

FIGURE 3. PERCENTAGE OF COUNTRIES REPORTING PATHOLOGY SERVICES GENERALLY AVAILABLE BY WHO REGIONS AND INCOME LEVEL



AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region; LIC: low-income countries; LMIC: lower-middle-income countries; UMIC: upper-middle-income countries; HIC: high-income countries
Source: 2017 NCD Country Capacity Survey (WHO 2018 (6)).

DESPITE ITS CRITICAL IMPORTANCE TO CANCER MANAGEMENT, THERE IS A SIGNIFICANT GAP IN ACCESS TO PATHOLOGY SERVICES AROUND THE WORLD.

In many low- and middle-income countries, even when pathology services do exist, they are often under-resourced with a lack of trained health workforce, functional equipment and quality supplies, leading to unreliable quality and delay in diagnosis. The common challenges in access to pathology services are described in Table 1.

TABLE 1. COMMON BARRIERS IN ACCESS TO PATHOLOGY SERVICES

KEY ELEMENTS	MAJOR CHALLENGES
Leadership and governance	• Low priority of pathology services in national health strategy • Absence of national laboratory policy and strategic plan • Inadequate or weak implementation of laboratory regulations • Absence of structured responsibility to monitor pathology services
Infrastructure and medical devices	• Absolute lack of pathology laboratory • Unregulated procurement and management of essential equipment and supplies • Lack of effective equipment maintenance systems • Lack of standardization and harmonization of operating procedures
Human resources	• Inadequate number of pathologists and other related workforce • Inadequate education, training and supervision programmes • Lack of strategic plan to retain staff • Lack of career structure and opportunities
Service delivery	• Weak or absent networking between pathology laboratories • Poor coordination with clinical services • Weak quality management system • Inadequate safety measures
Health information system	• Absence of laboratory information system • Insufficient collection of data • Inadequate use of data for laboratory quality and management
Financing	• Inadequate financing to invest in resources and infrastructure • Incentives for irrational use • Insufficient cost-effectiveness analysis

"Wilson et al. 2018 (4); WHO 2010 (5)".

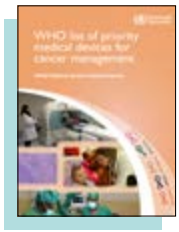
1.3 PURPOSE AND SCOPE

This guide is intended to assist programme managers and health officials understand pathology services and minimum requirements for establishing and maintaining a pathology laboratory with histopathology and cytopathology services. Although flow cytometry for immunophenotypical analysis of liquid tumours (e.g. leukaemia and lymphoma) is important in cancer, especially in paediatric tumours, this technology will not be addressed in this guide. Additional tools and resources to supplement this guide are provided in Box 1.

BOX 1. ADDITIONAL TOOLS AND RESOURCES

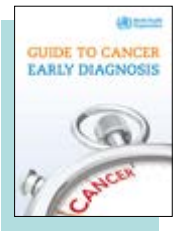
National cancer control programmes: policies and managerial guidelines (WHO 2002 (7))

Cancer control: knowledge into action (WHO 2008 (8))



List of priority medical devices for cancer management (WHO 2017 (3))

Laboratory quality management system: handbook (WHO 2005 (12))



Guide to cancer early diagnosis (WHO 2017 (9))

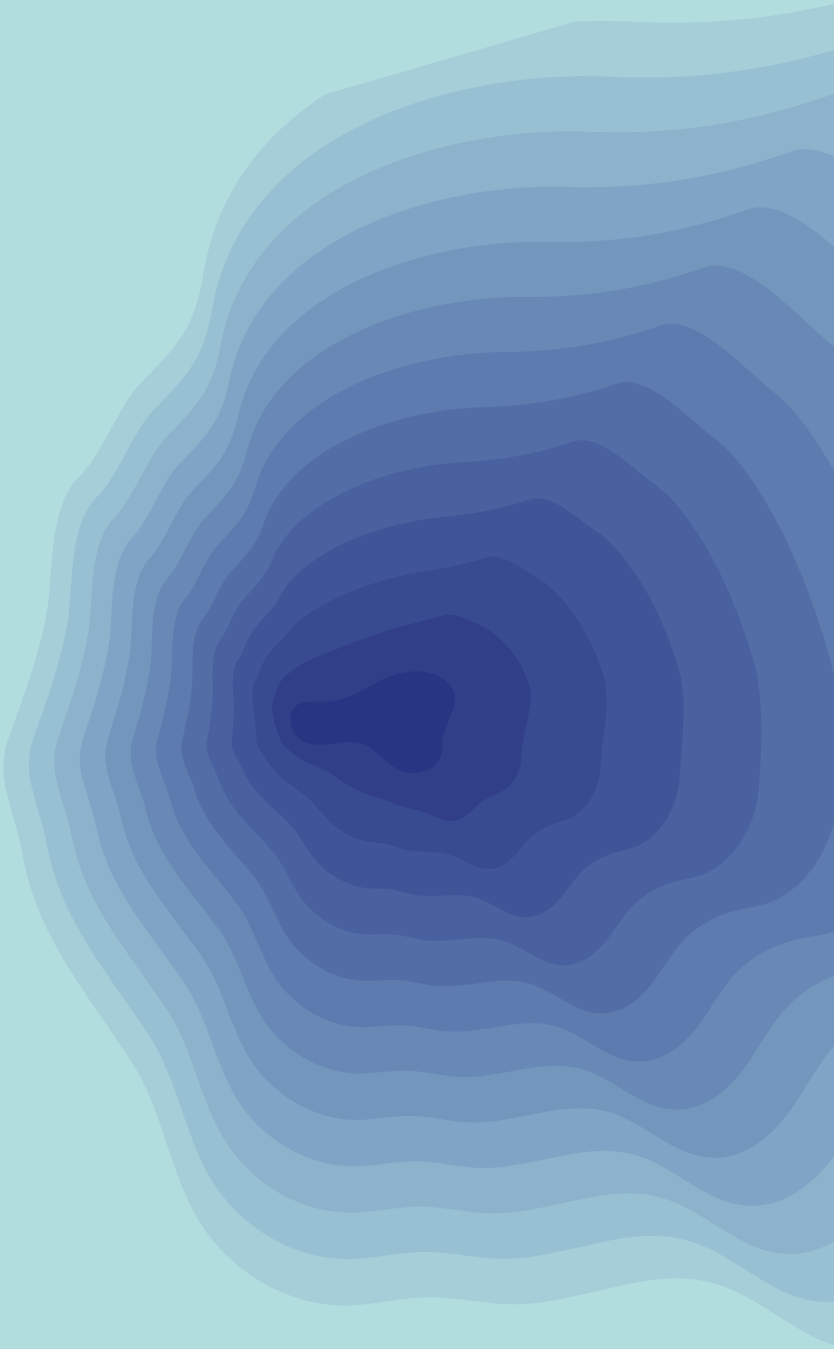
The selection and use of essential in vitro diagnostics (WHO2019 (13))

WHO Classification of tumours series (WHO (10))

WHO guidance on national health laboratory polices, strategies and tools to improve laboratory capacity (WHO (11))

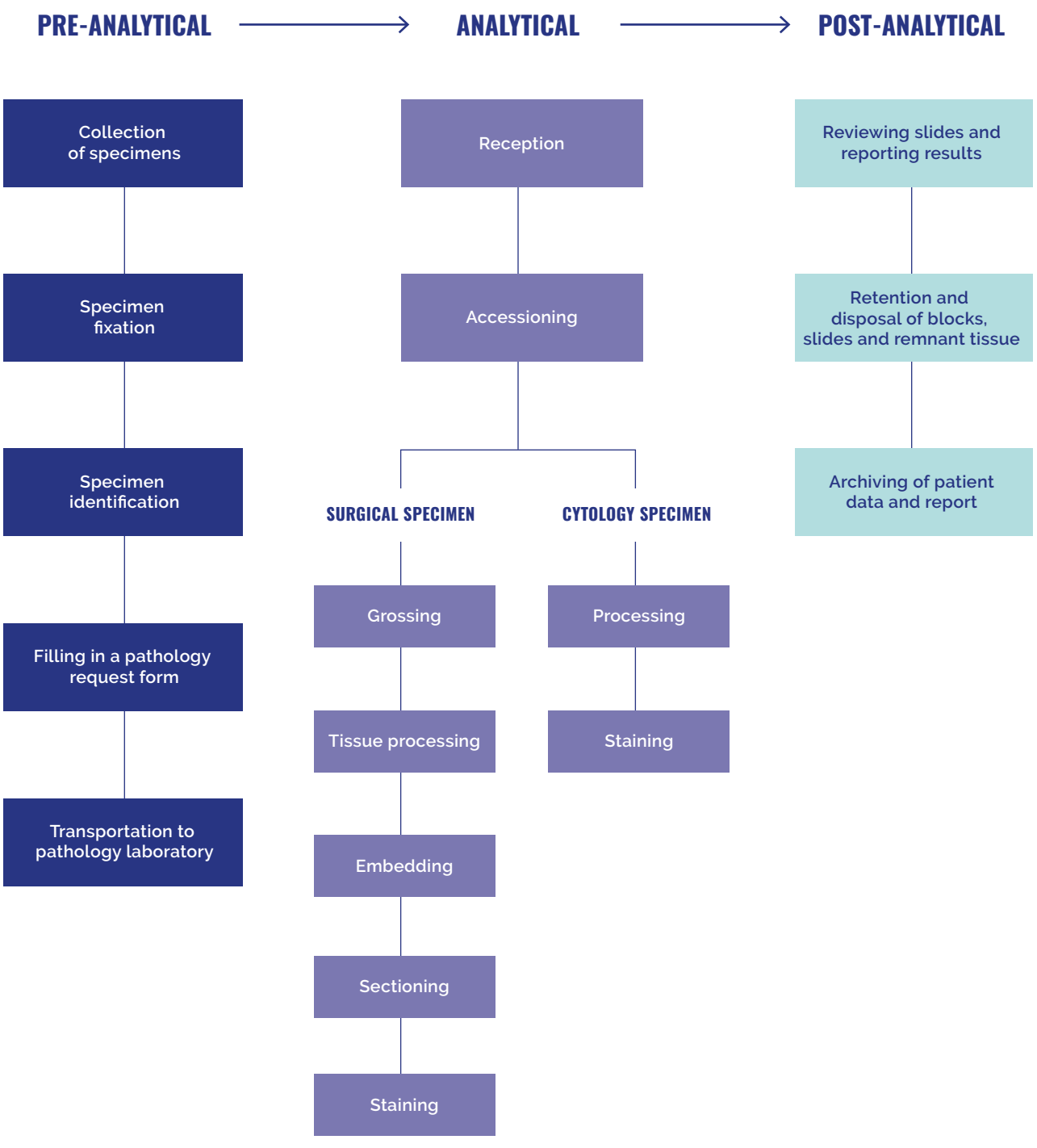
SECTION 2

UNDERSTANDING PATHOLOGY SERVICES



Pathology services consist of pre-analytical, analytical and post-analytical phases, each of which consists of multiple components according to the specimen management workflow (Figure 4). Although the components in the pre-analytical phase are the function of a clinical service, the pathology laboratory makes decisions about their standard measures as they affect the overall quality of pathology results.

FIGURE 4. THREE PHASES OF PATHOLOGY SERVICE AND THE SPECIMEN MANAGEMENT WORKFLOW



2.1 PRE-ANALYTICAL PHASE

2.1.1 COLLECTION OF SPECIMENS

The decision to collect specimens for pathological examination is made by physicians or nurses in clinical service with specialized knowledge of the disease and appropriate sampling method (Table 2). Inappropriate sampling can result in poor specimen collection and negatively influence the final diagnosis.

INAPPROPRIATE SAMPLING CAN RESULT IN POOR SPECIMEN COLLECTION AND NEGATIVELY INFLUENCE THE FINAL DIAGNOSIS.

TABLE 2. COMMON SAMPLING METHODS

	SAMPLING METHOD	EXAMPLE OF SITES
Surgical specimen	Core needle biopsy	Bone marrow, breast
	Endoscopic biopsy	Nose, sinus, gastrointestinal tract, bronchus, lung
	Minimally invasive surgical biopsy	Thoracic, abdominal and pelvic organs
	Surgical resection	Any organ
Cytology specimen	Smear	Cervix, vagina, vulva, gastrointestinal, pulmonary, skin
	Body fluids	Urine, sputum, bronchial washings, cerebrospinal fluid, pleural, peritoneal, pericardial, synovial fluids
	Aspirates	Bone marrow, any tumour (radiology-guided or blind)

2.1.2 SPECIMEN FIXATION

In most cases, specimens should be fixed to preserve them in a state as close to the living state as possible, and protect against shrinkage, autolysis or bacterial action.

Table 3 describes common fixation methods for surgical and cytology specimens. Different fixatives may be needed for specialized studies.

Specific considerations for fixation for certain tumours are required and should be addressed in the standard operating procedures (SOPs). For example, in breast tissue, the time the specimen has been placed in 10% NBF should also be recorded for calculation of the cold ischaemic time, which is recommended to be kept to less than one hour for immunohistochemical evaluation (e.g. oestrogen receptor, progesterone receptor, HER2 expression) (14).

Cold ischaemic time = [Time specimen placed in formalin] – [Time of collection]

TABLE 3. COMMON FIXATION METHODS

	FIXATIVE
Surgical specimen	10% neutral buffered formalin (NBF)*; the volume of the formalin must be 10–20 times the size of the specimen
Cytology specimen	95% ethanol or cytology fixative spray (for Papanicolaou staining) Air dry ± 100% methanol (for May-Grunwald Giemsa staining)

**See Annex 1*

Photo credit: Jeannette Guarner

2.1.3 SPECIMEN IDENTIFICATION

All specimens must be submitted in an appropriate container or slide, labelled with the patient's name, date of birth, unique identifier (e.g. hospital number), sampling site, date and time of specimen collection. The labels should be on the primary container (not the lid) and specimens from different sites or lesions from the same patient must be submitted in separate containers.

2.1.4 FILLING IN A PATHOLOGY REQUEST FORM

A pathology request form should be completed with all relevant information needed for the pathologist to make an accurate diagnosis (see Annex 2 and Annex 3). At a minimum these include:

- Patient details (e.g. name, date of birth, unique identifier)
- Details of the requesting service (e.g. name, contact number)
- Date and time of specimen collection
- Sampling site
- Clinical history and pertinent information
- Test requested.

An incomplete form may require the laboratory to reject and return the specimen unprocessed. As much clinical data as are available for a given patient should be provided to the pathologist; thus, direct, ongoing communications and/or a shared electronic medical record are crucial.

2.1.5 TRANSPORTATION TO PATHOLOGY LABORATORY

Frequently, specimens are collected at distant health-care facilities and transported to the pathology laboratory for subsequent processing and testing. Specimen transport networks capable of handling pathology specimens are crucial, because processing laboratories can only be placed, for cost and efficiency purposes, as a central laboratory for a given population size (e.g. at least 1 000 000 per laboratory). Transport of potentially hazardous materials must be managed carefully and adhere to regulations, including from:

- National transport regulatory bodies, including rail, road traffic and postal agencies
- International civil aviation organization, as conveyed by the International Air Transport Association (IATA)

Photo credit: Jeannette Guarner

2.2 ANALYTICAL PHASE

IT IS IMPORTANT TO HAVE ESTABLISHED LINES OF COMMUNICATION BETWEEN PATHOLOGY LABORATORY AND CLINICAL SERVICES.

2.2.1 RECEPTION

The receipt of specimens occurs at the laboratory reception, where it is ensured that every specimen received, including those from other facilities or laboratories in the network, is properly labelled with patient identification and clinical information and is appropriately fixed. Real-time control of all specimen movement into the laboratory is required to guarantee accurate documentation of all specimens and to ensure operational efficiency.

Rules for rejecting specimens of any type should be pre-determined by the pathology laboratory receiving specimens and provided to all clinicians and health-care facilities. Examples of specimens that should be rejected include (12):

- Unlabelled specimen
- Insufficient patient information
- Specimen label and patient name on the test request form do not match.

Examples of major issues that may influence the result include:

- Broken or leaking tube/container
- Inadequate volume for the quantity of preservative
- Prolonged transport time or other poor handling during transport.

It is important to have established lines of communication between pathology laboratory and clinical services to address lack of essential information when needed.

2.2.2 ACCESSIONING

When the specimen and request form is removed from the transport container, the identifiers on the request form and specimen must match. When all identifiers match, the specimen is accessioned and assigned a unique pathology number that is used to link the specimen to the patient and track the specimen through the various stages of processing in the laboratory. Barcoded labels increase the efficiency and accuracy of this process by allowing for real-time tracking of all parts of a case (gross tissue, blocks, slides, special stains, etc.) through the laboratory.

Photo credit: Jeannette Guarner

2.2.3 GROSSING, TISSUE PROCESSING, EMBEDDING, AND SECTIONING OF SURGICAL SPECIMEN

After accessioning the surgical specimen must be described, measured and dissected to fit into a tissue cassette for processing. The simplest gross description comments on colour, shape, texture and dimensions of the specimen. Any large specimen that requires slicing or dissection should have a complete description of the dissection, any findings within the tissue upon dissection, and a key to what is in each cassette. SOPs and/or the use of published standardized guides for the dissection and description of complex specimens are required to insure consistency and continuity.

The fixation process from formalin to paraffin is best done using an automated tissue processor. The specimen is then embedded in paraffin wax and tissue blocks are produced. The blocks are sectioned at five to six microns in thickness using a properly maintained microtome. The thin sections are floated on a warm water bath to allow for collection onto a glass slide.

2.2.4 PROCESSING OF CYTOLOGY SPECIMEN

Liquid cytology specimen requires centrifugation or filtration to separate cells. The cells are then deposited on a glass slide as a thin layer by sedimentation or application of pressure.

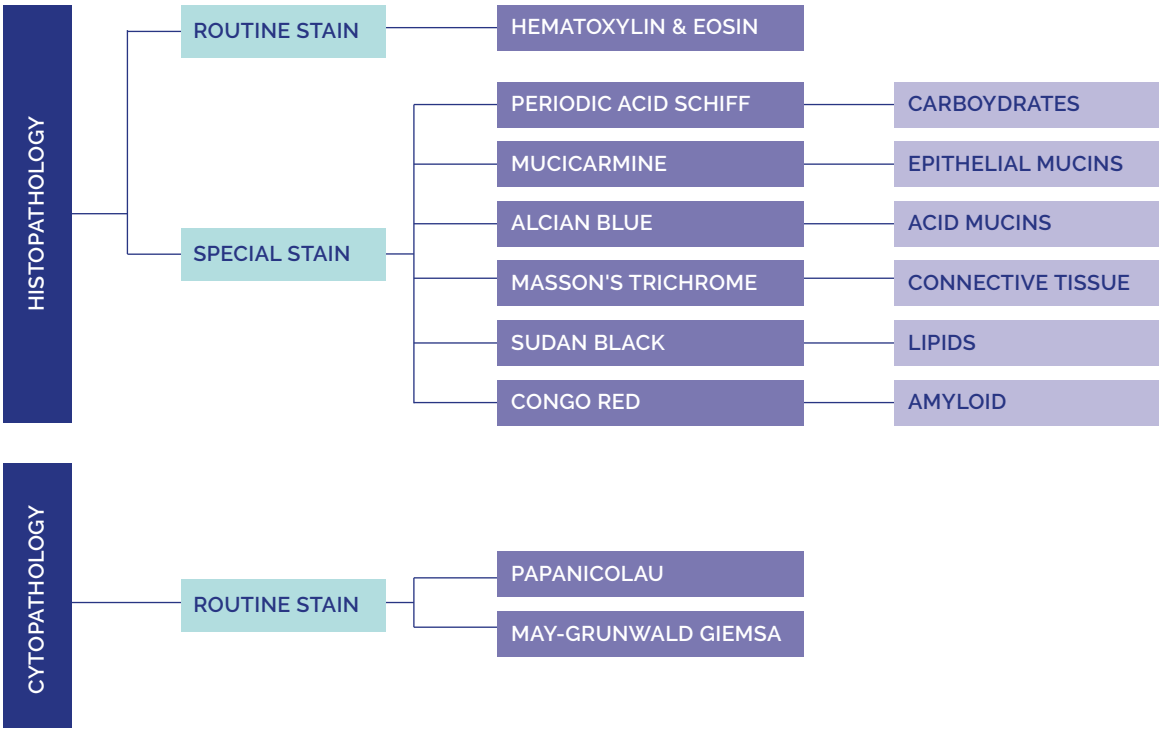
Photo credit: Mohana S. Narasimhamurthy.

2.2.5 STAINING

Once specimens are mounted on glass sides, rehydration and staining are needed for examination under a microscope. For histopathology, haematoxylin and eosin (H&E) stain is used as a routine stain and plays a critical role. Special stains and immunohistochemical stains are used when H&E does not provide all the information the pathologist needs. For cytopathology, Papanicolaou and May-Grunwald Giemsa stains are routinely used (Table 4).

After staining, slides are dehydrated, and covered by mounting media and thin cover glasses that harden and seal the preparation to make them permanent. Stained slides should then be collected in a slide assembly with the request forms for pathologists to review alongside the relevant data and information.

TABLE 4. SAMPLE STAINING METHODS



See Annex 4.
Sources: WHO 2017 (3); WHO 2019 (12)

2.3 POST-ANALYTICAL PHASE

2.3.1 REVIEWING SLIDES AND REPORTING RESULTS

The importance of providing comprehensive pathology reports cannot be overemphasized, because their accuracy is fundamental to treatment decisions and good outcomes. Reports should follow established guidelines and include diagnostic, prognostic and predictive information based on the submitted specimen type (15, 16).

In order to improve overall data reporting and retention for pathology, synoptic reporting should be used (16). Synoptic reporting is a clinical documentation method that uses a structured, electronic or paper report that captures each of the elements in a standardized way that can easily be gathered and organized for treatment and research purposes. The structured checklists help clinicians produce complete, consistent and valuable medical reports (see Annex 5).

Synoptic reports are quick to produce and easy to interpret. They also ensure consistency of reporting, help to prevent medical record errors, streamline clinician workflow and improve the quality of patient care. Additional benefits include:

- Improvement of turnaround times;
- Elimination of transcription costs;
- Streamlining report distribution;
- Consistently more complete reports, than those produced by dictation or free text writing;
- Reduction of subjectivity of interpretation;
- Ensuring that reports contain all of the information required for clinical decision-making;
- Presenting the data in a format that is easy to interpret (17).

Photo credit: Jeannette Guarner

2.3.2 RETENTION AND DISPOSAL OF TISSUE BLOCKS, SLIDES AND REMNANT TISSUE

Pathology departments have a vast number of paraffin blocks, slides and remnant tissue (i.e. the tissue left over after blocks and slides are made) that remain after the completion of pathology reports. Retention may be needed for future testing, second opinions or medicolegal purposes, and should be carried out in compliance with national regulations. In most cases, tissue blocks and slides must be maintained for a minimum of 10 years. Remnant tissue can be discarded 30 days after the case is signed out officially by the pathologist.

Written policies should be available and should include the following information:

- Retention time
- Location
- A system for storage organization (e.g. by day of receipt, by accession number)
- Disposal procedures.

2.3.3 ARCHIVING OF PATIENT DATA AND REPORT

Patient data and reports should be retained permanently. Older data may be electronically archived or records may be stored offsite as long as retrieval does not hinder patient care.

All patient records are confidential and access should be limited to authorized personnel only. Locked cabinets for paper records and security codes for electronic systems are required and laboratory staff must be trained on maintenance of privacy and confidentiality of patient records.

Photo credit: Mohana S. Narasimhamurthy

SECTION 3

PLANNING AND SETTING UP A PATHOLOGY LABORATORY

3.1 SITUATION ANALYSIS

RESULTS FROM THE ANALYSIS CAN INFORM THE NEEDS FOR PLANNING AND IMPLEMENTATION OF PATHOLOGY SERVICES.

When establishing a pathology laboratory, the process begins with a situation analysis of the relevant national policy, regulatory framework, service organization and an understanding the needs of pathology services within the geographical population. Results from the analysis can then inform the needs for planning and implementation of pathology services.

The assessment should engage a wide range of stakeholders, including hospital management, senior physicians of clinical departments and laboratory staff. Tools such as the WHO Laboratory Assessment Tool could assist in assessing the national laboratory system and individual laboratories, although adaptation would be needed to meet pathology specificities and local context (18). Annex 6 provides a sample questionnaire for rapid assessment of pathology services at the facility level.

3.1.1 NATIONAL HEALTH LABORATORY POLICY

A national health laboratory policy, if one exists, provides the overall framework and direction for establishing, strengthening and maintaining standards to be adopted by all laboratories in the country, in accordance with the overarching national health policy. It defines the regulatory framework, organizational and management structure, minimum standards of diagnostic services and human resource requirements at each level of a tiered laboratory network.

3.1.2 REGULATORY FRAMEWORK

A regulatory framework is the legal means of governing, controlling and ensuring competent performance of laboratory services in both public and private sectors. It is also responsible for licensing providers, setting national standards, monitoring performance and compliance with standards, taking disciplinary action for non-compliance, and setting requirements for pre-service training and continuing professional development for health laboratory personnel.

Photo credit: Jeannette Guarner

3.1.3 SERVICE ORGANIZATION

Laboratory services are commonly organized within a tiered laboratory network, in which a designated national reference laboratory supports regional- and peripheral-level laboratories (Figure 5). Centralization of testing allows operational efficiencies with pooling of scarce resources and helps promote the implementation of uniform standards. It is necessary to assess which type of laboratories already exist and what services are being provided, and consider the needs of pathology services in the new laboratory.

National reference laboratory and regional laboratories

A national reference laboratory is usually situated in a cancer centre while regional laboratories are usually located in tertiary hospitals dedicated to cancer treatment in the regions. They provide a wide range of tests available and serve as central laboratories to which lower-level facilities refer samples and training staff. A national reference laboratory is responsible for quality assurance, forecasting needs for all laboratories in the network, and ensuring that reagents and consumables purchased centrally are tested, validated and made readily available to all laboratories. It also provides or coordinates external quality assessment (EQA) services, and communicates internally within the network and externally with international collaborating agencies.

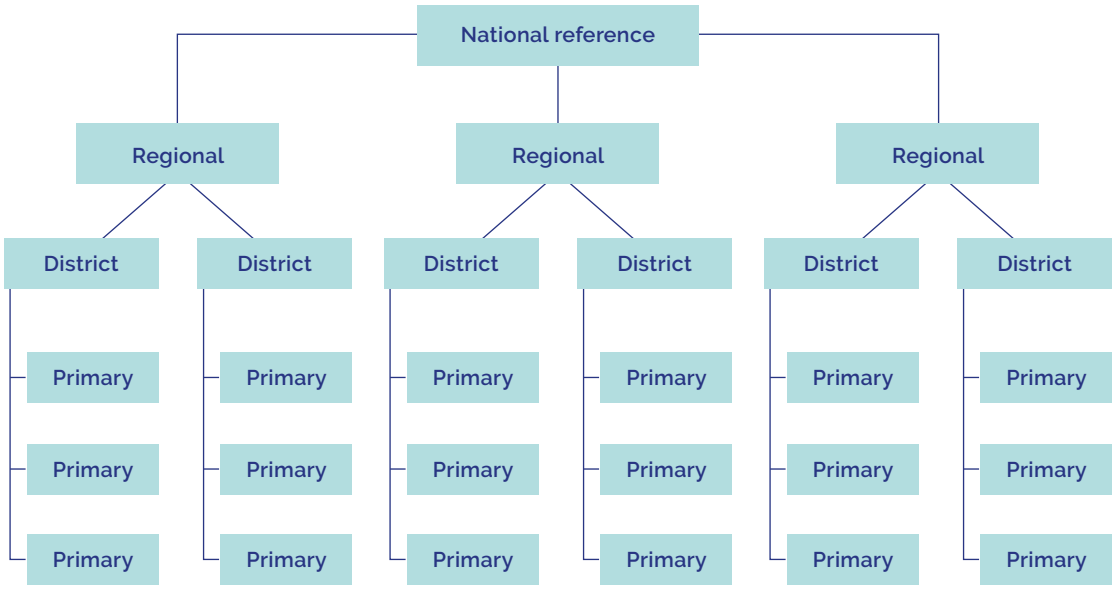
District laboratories

District laboratories provide pathology services and may refer samples or patients to the national reference laboratory when they do not have the capacity to process samples, or when in need of consultation of difficult cases. They serve as the link between peripheral laboratories and the national reference laboratory.

Primary laboratories

Primary laboratories are located at the patients' first point of contact within the health system. Rather than processing samples onsite, they often only collect samples and refer them to the regional laboratory within the network.

FIGURE 5. ILLUSTRATIVE EXAMPLE OF TIERED LABORATORY NETWORK



Source: Adapted from WHO 2013 (19).

3.2 BASIC RESOURCE REQUIREMENTS FOR A PATHOLOGY LABORATORY

ESTABLISHING A PATHOLOGY LABORATORY REQUIRES INVESTMENTS IN PHYSICAL INFRASTRUCTURE, EQUIPMENT, SUPPLIES, REAGENTS AND HUMAN RESOURCES.

In general, a pathology laboratory should be established as part of the laboratory complex within a hospital, rather than a standalone laboratory. When planning the physical location of the pathology laboratory in a hospital, it is important to consider its accessibility to the operating room, from which surgical specimen may be transferred (e.g. intraoperative gross consultation).

Establishing a pathology laboratory requires investments in physical infrastructure, equipment, supplies, reagents and human resources. Estimating operating costs and allocating sufficient funds are also critical for establishing and maintaining a laboratory service.

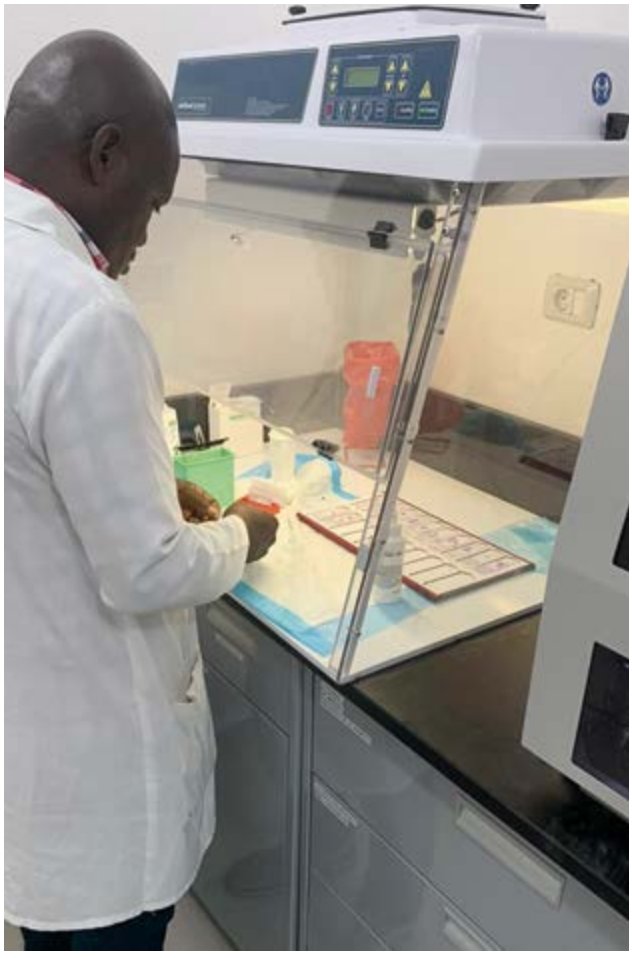


Photo credit: Linda Cherepow

3.2.1 PHYSICAL INFRASTRUCTURE AND SAFETY

For safe and efficient operation, a pathology laboratory requires sufficient space and ventilation, electrical system, lighting, water, sanitation, storage, safety, security and communication tools (Table 5) (3).

TABLE 5. INFRASTRUCTURE REQUIREMENTS

INFRASTRUCTURE	MINIMUM REQUIREMENTS
Ventilation and air conditioning systems	• Appropriate ventilation with adequate humidity and temperature conditions • Specific ventilation installed in areas where biohazardous materials (e.g. formalin) are being handled
Electrical system	• Continuous and uninterrupted electrical supply of appropriate electrical voltage • Back-up electrical supply for essential equipment, in case of power failure
Lighting	• Adequate lighting with maximum use of natural light
Water	• Deionized or filtered water
Sanitation	• Walls, ceilings and floors made of a material suitable for regular cleaning and resistant to a potential biohazardous material spill
Storage	• Storage of supplies and reagents, residual tissues from specimens, tissue blocks and glass slides
Safety	• Safety considerations for biohazardous materials, flammable materials, toxic materials and waste
Security	• Access to the laboratory restricted to authorized staff only
Communication tools	• Telephones, computers and access to electronic networks

Source: WHO 2017 (3).

Photo credit: Jeannette Guarner

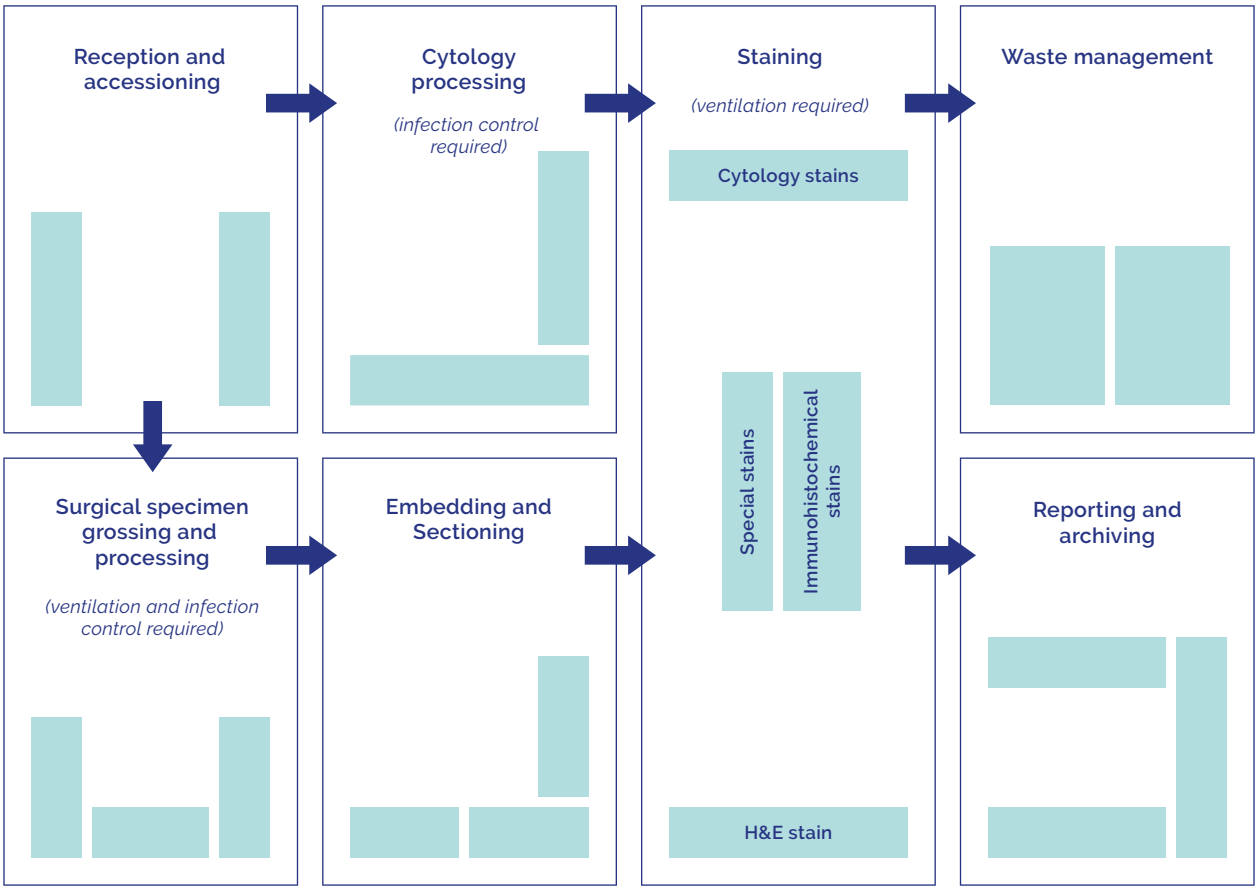
Space layout

Space layout should be organized and arranged based on the workflow of the laboratory so that there is maximum efficiency and minimum crossing of paths at different points in the handling process (Figure 6).

Space could be divided into seven major areas:

- Reception and accessioning area.
- Surgical specimen grossing and processing area; a ventilator or well-ventilated environment must be set up for the use of formalin and the space must be treated as an infection control area.
- Embedding and sectioning area.
- Cytology processing area; the space must be treated as an infection control area.
- Staining area; a fume food or well-ventilated environment must be set up for the use of xylene and methanol.
- Reporting and archiving area.
- Waste management area.

FIGURE 6. EXAMPLE OF SPACE LAYOUT



Source: Adapted from Mullay et al. 2017 (20).

Safety concerns

Laboratory service must be free from recognized biological, chemical and physical hazards that may cause serious harm to the staff, public or environment. The greatest risk to the public and environment is associated with wastes from pathology processes. Properly handling these wastes, protecting water supply primarily through recycling and adequate disposal are essential.

Receipt and handling of fresh specimens carries the highest risk for staff. Universal precautions and personal protective equipment (PPE) must be required for handling potentially infectious specimens, needles and sharps, and chemicals such as formalin. For example, surgical specimens (e.g. ovarian tumour) can contain large collections of unfixed blood or other fluids and should be carefully opened in a controlled environment with PPE.

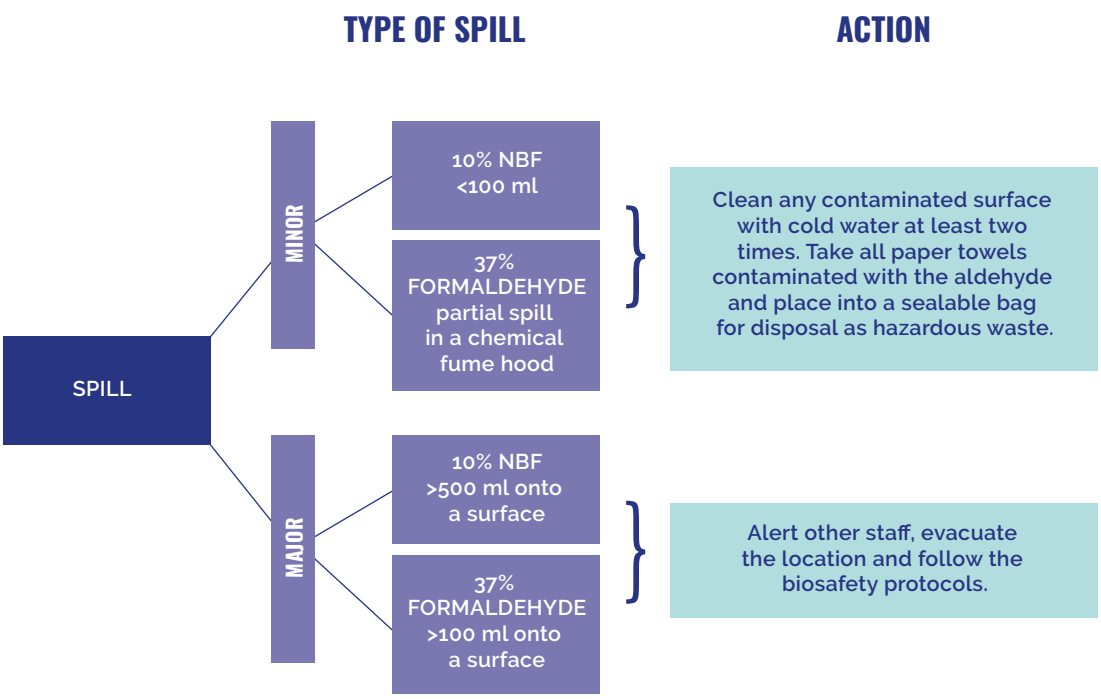
Laboratory personnel must be trained and aware of potential hazards and safe handling of such materials. Occupational safety and health standards should be established, and compliance must be mandatory.

Management of chemical hazard spills

Formalin, alcohol or xylene spill is not rare and can present a hazard through inhalation, direct skin or eye exposures. A spill is considered to be minor if it can be cleaned up quickly by laboratory personnel who have received training on the hazards of laboratory chemicals (21). The quantity, concentration, location of the spill and availability of staff may elevate some spills to the status of a major spill, which requires help from outside the laboratory group.

A pathology laboratory must have a written procedure in place for safe handling, including clean-up of formalin spills. Table 6 describes examples of spill scenarios and suggested actions to minimize potential exposures.

TABLE 6. EXAMPLES OF FORMALIN SPILL SCENARIOS AND SUGGESTED ACTIONS



Source: Adapted from University of Rochester (21).

3.2.2 EQUIPMENT

List of essential equipment

A pathology laboratory requires appropriate and functioning equipment to conduct quality testing. Table 7 describes the essential equipment required for histopathology and cytopathology (3).

Selecting equipment

Selecting the most appropriate equipment for the laboratory is important. Some criteria to consider when selecting laboratory equipment include:

- compliance with infrastructure requirements (e.g. uninterrupted power supply, constant voltage, level of humidity, constant room temperature);
- type of procedures and estimated workload;
- ability to ensure maintenance in accordance with manufacturers' recommendations and timely service;
- availability and competency of human resources;
- alignment with the availability and complexity of diagnostic and treatment procedures; and
- ability to ensure adequate quality assurance and safety.

Acquiring equipment

Since major equipment constitutes a large capital expenditure for a laboratory, options should be explored for purchasing or leasing, along with sourcing relevant consumables, accessories, service contracts for maintenance, and software (3). Choosing equipment to be manual, semi- or fully automated depends on the volume of tests and resources available to a laboratory. The number of each equipment type should be based on the need for redundancy (e.g. expected long service times), expected volume of the laboratory and number of personnel.

In resource-limited settings, sometimes it is more cost effective to consider rental agreements for expensive items of equipment. When making this decision, it is important to factor in repair costs and service contracts – the initial cost of an instrument may seem reasonable, but it could be expensive to repair. The equipment also depreciates annually and would eventually have to be replaced.

Many pieces of equipment are engineered and manufactured assuming certain parameters, such as uninterrupted power supply, consistent and constant voltage and stable ambient temperature. Technical specifications of equipment should be checked against existing conditions prior to procurement to ensure compliance.

TABLE 7. MINIMUM ESSENTIAL EQUIPMENT

HISTOPATHOLOGY

- Reception table
- Grossing station
- Fume hood chamber
- Refrigerator
- Tissue processor
- Tissue embedding unit
- Microtome
- Cryostat
- Reagent recycler
- Water bath
- Hot plate
- Laboratory oven
- Organ balance
- Mechanical balance
- Autostainer
- Binocular light microscope
- Computer and printer
- pH meter (probe)
- IHC system (automated or manual)

CYTOPATHOLOGY

- Cytocentrifuge
- Centrifuge
- Refrigerator
- Autostainer
- Binocular microscope
- Computer and printer

Source: WHO 2017 (3).

Photo credit: Yasuyo Matsumoto

In some settings, countries rely on donated supplies and equipment; however, these may not necessarily respond to local needs. In general, donated equipment should include a donated service contract or service package to be of most value. Decisions on purchase of the second-hand equipment and acceptance of donated equipment should always consider a number of indicators on suitability, including running and maintenance costs (see Annex 7) (22,23). Recipients may not always understand training material in the donor's language, or the subject matter may not be appropriate. Training of local biomedical engineers or laboratory equipment experts by the manufacturer or expert users is highly recommended.

Installation of equipment

Whenever possible, installation of equipment should be done by the manufacturer. The following details should also be addressed before putting the equipment into use (13):

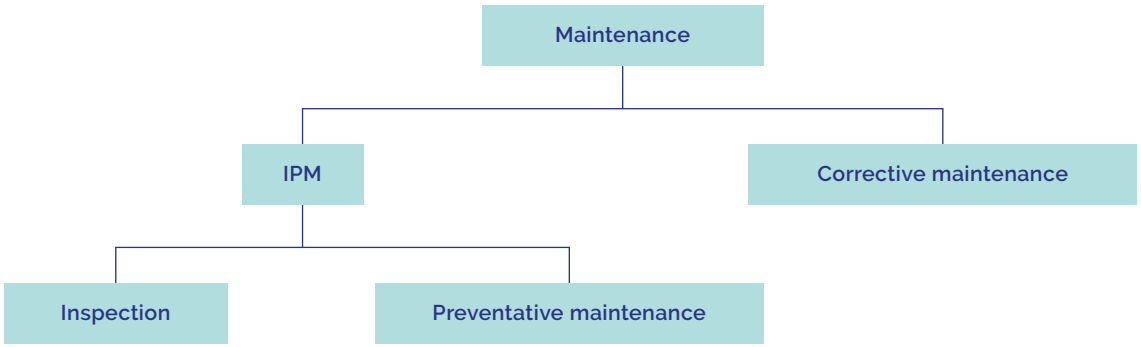
- Assign responsibility for performing maintenance of the equipment;
- Develop a system for recording the use of parts and supplies;
- Implement a written plan for calibration, performance verification and proper operation of the equipment;
- Establish a scheduled maintenance plan that includes daily, weekly and monthly maintenance tasks; and
- Provide training for all operators; only personnel who have been trained should be authorized to use the equipment.

Maintenance of equipment

Non-functioning equipment is common in resource-limited settings, compounded by insufficient financing to repair and/or a lack of technical expertise to make repairs. Maintenance can be divided into inspection and preventative maintenance (IPM) and corrective maintenance (Figure 7) (24). IPM is scheduled activities that includes inspection to verify proper functionality and safe use of a device, and preventive maintenance to extend the life of a device and prevent failure (e.g. calibration, spare part replacement, cleaning). Corrective maintenance is unscheduled activities to restore the physical integrity, safety and performance of a device after a failure.

Ensuring maintenance of equipment would result in a high level of performance and greater confidence in the reliability of results, fewer interruptions of services due to breakdowns, lower repair costs and increased safety and productivity. Biomedical engineers serve a critical role in maintenance of equipment and optimizing existing resources.

FIGURE 7. COMPONENTS OF EQUIPMENT MAINTENANCE



Source: WHO 2011 (23).

3.2.3 SUPPLIES AND REAGENTS

List of essential supplies and reagents

The operation of a pathology laboratory depends on the availability of supplies and reagents to meet the testing needs. Requirements for reagents and consumables would vary with the tests being performed. Table 8 lists an example of priority supplies and reagents for histopathology and cytopathology.

TABLE 8. SAMPLE LIST OF PRIORITY SUPPLIES AND REAGENTS FOR HISTOPATHOLOGY AND CYTOPATHOLOGY

	HISTOPATHOLOGY	CYTOPATHOLOGY
Instruments	• Forceps • Knife for large specimens • Scissors • Spatula • Knife sharpener • Scalpel handle with blades	• Needles and syringes for fine needle aspiration biopsy • Forceps
Personal protective equipment (PPE)	• Medical coat • Protective gowns aprons • Face masks • Examination gloves, latex • Non-sterile, single use syringe	• Medical coat • Face masks • Gloves, examination, latex • Non-sterile, single use syringe
Disposables/ medical supplies	• Low-profile blades for microtome • Brush • Compress, gauze, sterile and non-sterile • Cover glass • Glass slides • Markers, fine point, permanent black • Scalpel blades • Specimen bags • Sponges • Tissue or paraffin blocks or cassettes • Paper towels	• Cover glass • Compress, gauze, sterile and non-sterile • Glass slides • Markers for glassware • Sponges • Pipette • Syringes and needles (various sizes) • Swab-pad • Paper towels • Wooden or plastic applicator sticks
Utensils	• Strainer • Ruler or measuring tape • Cutting board • Cassette cabinet • Slides cabinet • Beaker • Bottle • Reagent bottle • Bunsen burner	• Biosafety cabinet • Slides cabinet • Basket for slides • Beaker • Bottle • Reagent bottle • Bunsen burner • Container for hazardous wastes • Coplin jar

	HISTOPATHOLOGY	CYTOPATHOLOGY
Utensils (continued)	• Container for specimen immersion • Coplin jar • Erlenmeyer flask • Flat bottom flask • Funnel • Graduated cylinder • Graduated pipettes • Laboratory mortar • Pasteur pipette • Rack, staining slides • Specimen cup • Staining boxes • Wash bottle	• Flask • Funnel • Graduated pipettes • Pasteur pipete • Petri dish • Micropipettes • Laboratory mortar • Rack, drying glass and plasticware • Tube racks • Staining slides rack • Safety box for used syringes/needles • Specimen cup • Sample container
Reagents and solutions for stains	**Routine processing** • 10% NBF • Xylene • 100%/95% Alcohol • Melted paraffin wax **H&E stain** • 100%/95%/80%/70% Alcohol • Xylene • Harris's haematoxylin • Eosin • 0.25% Acid alcohol • 20% Sodium acetate • Distilled water **Special stain** • Harris's haematoxylin • Eosin • 0.5% Periodic acid • Schiff reagent • 3% Acetic acid • Alcian blue • Sodium chloride • Sodium hydroxide • Bouin fixative • Acid fuchsin • 5% Phosphotungstic acid • Light green • Sudan black B • Propylene glycol • Weigert's iron haematoxylin • Biebrich scarlet • Carmine • Congo red	**Papanicolaou stain and Giemsa stain** • 100%/95%/80%/70%/50% Alcohol • Distilled water • Haematoxylin • Eosin • Orange Gelb-6 • EA50 or EA65 • May-Grunwald solution • Giemsa solution • 0.5% Acid alcohol • Methanol • Xylene

** Alternative processing methods such as the microwave-based method use a single proprietary solution that has shorter processing times.*
Source: WHO 2017 (3).

Inventory management

Inventory management is a key component of a laboratory service, as laboratory efficiency and productivity are compromised when supplies and reagents run out or expire (25,26). It is critical to ensure that appropriate quantities of supplies and reagents are always available, and wastage is prevented. The challenge is balancing the availability of supplies and reagents in stock with their expiration dates. Where possible, recycling of reagents such as formalin, xylene and alcohol could cut costs, prevent stockouts and decrease waste handling. Recycling requires specialized equipment with a low capital cost but translates into enormous cost and time savings overall.

An inventory management system enables a laboratory to closely monitor the condition and available quantities of all supplies and reagents, and be alerted when there is a need to reorder. The system could be set up by taking the following steps (12):

- Assign responsibility;
- Analyse the needs of the laboratory;
- Establish the minimum stock needed for an appropriate time period;
- Develop forms and logs;
- Establish a system for receiving, inspecting and storing supplies; and
- Maintain an inventory system in all storage areas, and for all supplies and reagents.

To analyse the needs, the laboratory should make a list of all the tests it performs and identify the supplies and reagents that are needed with the following information:

- A complete description of each item;
- The package count or number of units in which the item is supplied (e.g. Pipette tips could be packaged as 100 per box or 1000 per box);
- The approximate usage per month (e.g. six boxes used per month);
- The priority or importance level the item has in doing the work of the laboratory (e.g. used every day or only once a month);
- The length of time required to receive a delivery; and
- Storage space and conditions.

3.2.4 HUMAN RESOURCES

Staffing requirements

Health workforce is the most valuable resource in the laboratory system. The recommended occupation of providers and their competencies are listed in Table 9. Depending on national context, different occupations could fulfil each role.

Education, training and retaining health workforce

Maintaining an adequate number of qualified staff is critical to providing timely and accurate pathology services. It is important to ensure qualifications and certification through appropriate education, training and continuing professional development as identified by the national standards of the country. An effective supervision and mentoring programme could be developed at the central level to impart pre- and in-service training, support and monitor operations in all the network tier laboratories. Interdisciplinary coordination and teamwork with clinical services should also be encouraged (e.g. become a part of the breast cancer working group) (27).

In addition to training of pathology staff, there is a need for clinicians and nurses to be instructed about the need for appropriate and timely fixation of the tissues, and appropriate handling of the tissues in the appropriate fixative solutions (3,22).

Photo credit: Yasuyo Matsumoto

TABLE 9. STAFFING REQUIREMENTS

OCCUPATION	COMPETENCIES
Biomedical laboratory scientist (pathology laboratory technician)	Tissue assessment, processing, sectioning and staining
Anatomic pathologist	Analysis of pathology specimens with diagnosis
Biomedical engineer (biomedical technician)	Management of medical devices (planning and procurement) Supervision or performance of installation, users training, maintenance and decommissioning
Laboratory quality manager (anatomic pathologist, biomedical laboratory scientist)	Ensure quality control of all procedures, ensure that relevant SOPs are followed and that all staff maintain professional standards and certification Ensure that sufficient internal and external quality control procedures are in place and followed Provide employees with orientation and training Include policies relevant to personnel in the quality manual
Clerical support worker	Administrative tasks (reception, accessioning, secretarial support)

Source: WHO 2017 (3).

3.2.5 COSTING AND FINANCING

The challenge in establishing a pathology laboratory is that the testing performed has many cost inputs (equipment, consumables, personnel) compared with those at clinical laboratories. The following formula should be considered when determining costs for a pathology laboratory.

Total operating cost = [costs of consumables] + [cost of personnel] + [cost of equipment] + [general overhead] – [revenue from public sector funds] – [revenue from other third parties including patients]

The cost of consumables could be calculated based on local-source prices and bulk buying (for shelf-stable products); and sole-source prices, recurring supply costs, and shipping (for consumables with a finite shelf life). National, regional or multicountry programmes could be leveraged to negotiate prices with suppliers for high-cost, low-volume items for access to goods at a reasonable cost and at a lower cost than if purchased by a laboratory on its own.

The cost of laboratory personnel depends on a variety of factors, including levels of multitasking, breadth of laboratory services, cross-training and management structure with the laboratory.

Capital purchases of laboratory equipment should be accounted for in the initial budget, with equipment maintenance to ensure continued operation occupying a portion of subsequent annual budgets.

General overhead costs encompass the use of physical space in the facility (electricity, water, facility administrative costs) and should be reflected in annual budgets accordingly.

As a counter to laboratory costs, revenue from third parties include funding directly from the Ministry of Health and/or Ministry of Finance to support publicly supported patient care, income from donors for specific programmes (in kind or cash), revenue from insurance schemes that pay on the patient's behalf for

specific services and revenue from patients, in which direct charges are paid out of pocket by the patient for specific services. Table 10 breaks down each component, as well as the types of costs and methods of efficiency in costs.

In all cases, equity should be maintained in services provided; that is, all patients presenting to a facility regardless of funding source or classification, should receive the exact same level of quality care. To maintain this equity, revenue sources must be carefully explored by the facilities to understand the payer–mix ratios of the population.

TABLE 10. TYPE OF COSTS AND EFFICIENCY MEASURES

COSTS	SAMPLE ELEMENTS	SAMPLE EFFICIENCY MEASURES
Personnel	• Biomedical laboratory scientists • Pathologists • Clerical support workers • Biomedical engineers	• Cross-training across multiple laboratory tasks • Minimal management numbers • Centralized/single staff regulatory and quality management • General and sub-specialty training and practice • National (or regional) collaborating networks of laboratories and pathologists • Role delegation and task shifting • Supportive supervision
Equipment	• Initial capital costs • Equipment service contracts • Equipment preventative maintenance	• Rental or lease agreements • Initial service contract inclusion X multiple years • Onsite, trained personnel for preventative maintenance • Onsite, trained personnel for equipment repair and troubleshooting
Consum-ables	• Standard medical products • Special shelf-stable products • Special finite products	• Bulk buying of standard products • Recycling of bulk reagents (formalin, xylene, alcohol) • National (or regional) pricing schemes • Warehousing with rolling stock supply • Organization of laboratory services in tiers
General overheads	• Electricity • Water supply • Facility administration • Laboratory cleanliness and waste management	• Renewable energy sources (solar) • Rooftop water reservoirs • Onsite water treatment facilities • National (or regional) waste disposal plans
Revenue from public sector funds	• Direct government funding	• Continuous review of costs and reductions in costs • Multiyear active recruitment of funds with reporting
Revenue from other third parties including patients	• Direct donor funding • Social insurance schemes • Patient out-of-pocket costs and fees	• Tiered system based on income • Mutual incentive or benefit programmes • Instalment payments to facility • Value-based pricing informed by health technology assessment • Supplemental pricing across services

SECTION 4

QUALITY MANAGEMENT OF A PATHOLOGY LABORATORY

4.1 OVERVIEW

Since pathology results could have a direct impact on treatment and health outcomes of patients, they must be as accurate as possible. Quality does not happen by chance. A quality management system should be set up to facilitate coordinated activities to direct and control an organization with regard to quality (12, 16, 28).

The quality management system of any laboratory, including pathology, could be divided into 12 quality system essentials (Figure 8) (12). To ensure quality throughout the laboratory operations and achieve accurate, reliable and timely pathology results, all 12 essentials must be addressed. The *WHO Laboratory quality management system: handbook* describes each component in a concise and comprehensive manner (12), and should be referenced when establishing a pathology laboratory.

Four of the essentials (i.e. facilities and safety; equipment; purchasing and inventory; and personnel) are discussed in Sections 2 and 3. In this section, other components important for the operation of a pathology laboratory are presented.

FIGURE 8. TWELVE QUALITY SYSTEM ESSENTIALS

Source: WHO 2005 (12).

4.2 ORGANIZATION

It is the commitment and responsibility of the hospital manager to develop and implement the quality management system and ensure allocation of appropriate resources. A pathology laboratory should have a designated quality manager, and all staff must be properly trained on all aspects of the quality system and standards. Responsibilities of the quality manager would include:

- Monitoring all aspects of the quality system;
- Developing and updating SOPs;
- Ensuring staff are following quality policies and procedures;
- Regularly reviewing all records;
- Organizing internal audits and coordinating external audits; and
- Informing management on all aspects of the quality system monitoring.

4.3 DOCUMENTS AND RECORDS

4.3.1 STANDARD OPERATING PROCEDURE (SOP)

An SOP is a document with written step-by-step instructions of a procedure conducted in the laboratory (12). A pathology laboratory would have many SOPs, one for each procedure.

An SOP should include the following information and updated as needed:

- Title – name of the test;
- Purpose – include information about the test (why it is important, how it is used and whether it is intended for screening, to diagnose or to follow treatment and if it is to be used for public health surveillance);
- Instructions – detailed information for the entire testing process;
- Name of the person preparing the SOP; and
- Signatures of approving officials and dates of approval.

4.3.2 RECORDS

Records are laboratory information such as a specimen logbook, registers, laboratory workbooks, equipment maintenance records, quality control data, patient test reports, and results of internal and external audits. They are permanent (i.e. should not be revised or modified) and are used for tracking, monitoring, evaluating and managing pathology services.

4.4 PROCESS CONTROL

Process control refers to control of the activities employed in handling of specimens and examination processes in order to ensure accurate and reliable testing (12). It includes specimen management (discussed in Section 2) and quality control of the pre-analytical, analytical and post-analytical processes.

The concept of quality control in histopathology and cytopathology has some inherent challenges such as the lack of objective numerical data, subjective interpretation and bias, and non-uniformity of reporting patterns (29). Therefore, it becomes essential that the key activities for quality control are carefully conducted and monitored, including:

- Maintenance and care of reagents and solutions to prepare good quality slides for microscopic examinations:
  - *Some reagents and solutions can be purchased commercially, but others may need to be prepared in the laboratory following an established SOP. Once they are made, the bottles must be labelled with the name of the stain, concentration, date prepared, date placed in service, expiration date and name of the preparer, and stored properly at the correct temperature and protection from light.*
  - *As some stains can deteriorate and lose their ability to produce the correct reactions, they should be checked each day with positive and negative quality control materials according to a defined SOP. A record of the staining character should be maintained.*
  - *Stains should be checked regularly for precipitation or crystal formation, and bacterial contamination.*
- Use of good quality paraffin with an appropriate melting point for impregnation and embedding.
- Daily recording of the temperature of the paraffin bath, water floatation bath and slide warming table.
- Calibration of equipment as per manufacturer's instructions.

4.5 INFORMATION MANAGEMENT

4.5.1 INFORMATION MANAGEMENT SYSTEM

An information management system incorporates all the processes needed for effective management of patient information (12). The system can be entirely paper based, or it can be partly paper based with some computer support, or it may be entirely computerized. Although establishing a computerized laboratory information system requires infrastructure, computer hardware and software, trained manpower and utilities, it enables timely provision of pathology reports to clinical services and supports decision-making in case management as well as planning of resources (30).

The information management system could be part of the standalone laboratory system, or be integrated with a larger hospital information system. Direct extraction of data from standalone or hospital systems to national resources, including cancer registries, is extremely valuable.

4.5.2 CODING OF DISEASE

Accurate recording of diagnosis of diseases could enable countries to ascertain whether certain patterns of disease exist, such as higher incidence of a particular cancer in certain geographic areas of the country or in specific ages. These findings could then be investigated to determine whether underlying triggers are present and could be eliminated, or their impact lessened.

The requirement for coding is to first ascertain whether the specimen in question is malignant, in situ, benign or of uncertain histologic behaviour. The WHO International classification of diseases, 11th revision (ICD-11) contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases (31).

For neoplasms, the WHO International classification of diseases for oncology (ICD-O) has been internationally recognized as the definitive classification (32). Cancer registries throughout the world use it to record incidence of malignancy and survival rates, and the data produced are used to inform cancer control, research activity, treatment planning and health economics. The classification of neoplasms used in ICD-O links closely to the definitions of neoplasms used in the WHO Classification of tumours series (10), compiled by consensus groups of international experts and, as such, the highest level of scientific evidence and opinion underpins the classification.

4.6 OCCURRENCE MANAGEMENT

Occurrence management is a process by which errors or near errors are identified and handled, and is an integral part of laboratory quality management (12, 33). The goal is to correct the identified errors and to change processes to prevent the error from recurring (Table 11).

TABLE 11. COMMON SOURCES OF ERROR AND THEIR MANAGEMENT

ERROR	MANAGEMENT
Pre-analytic phase	
Collecting the wrong specimen	• Clinician education and awareness of SOPs of laboratory
Mislabelling/failing to label the specimen	• Clinician education and awareness of SOPs of laboratory
Storing and fixing the specimen incorrectly	• Clinician education and awareness of SOPs of laboratory
Transporting the specimen under conditions that damage it or endangers staff and public safety	• Clinician education and awareness of SOPs of laboratory
Analytical phase	
Error in specimen accession and identification	• Secondary check of accessioning process • Use of barcode technology
Wrong identification of anatomic location and as laterality of biopsy (right/left)	• Clinicopathological correlation and clearly written SOP
Lost specimens	• Record the number of specimens received in the laboratory daily and check against the clinical log of sent specimens

ERROR	MANAGEMENT
Lost specimens	• Record the number of specimens received in the laboratory daily and check against the clinical log of sent specimens
Inadequate volume/size, gross description, sampling, erroneous measurements	• Clearly written SOP and use of standardized grossing processes as found in published manuals
Extraneous tissue (floaters)	• Planned changing of chemicals used for processing based on the number of tissues passed through
Improper sections/inadequate serials	• Use paraffin of good quality with an appropriate melting point for impregnation and embedding • Use equipment of standard quality and calibrated at periodic intervals • Periodic calibration of the micrometer should be made to ensure consistency of section thickness • Proper maintenance of the knife (use of disposable blades is recommended) • Record temperature of the paraffin bath, water floatation bath and slide warming table on a daily basis
Damaging reagents or test kits by storing them improperly	• Clearly written SOP and storage guidelines followed
Using reagents that have been improperly stored, or after their expiration date	• Staff training and clearly written SOP
Poor staining and mounting quality	• Daily usage of controls for routine and special stains
Staff unclear who is responsible for carrying out a task, so it remains undone	• Staff training
Post–analytical phase	
Failing to follow an established algorithm for reporting	• Staff training and clearly written SOP
Reporting of results when the quality of specimen is out of range	• Staff training and clearly written SOP
Making a transcription error when preparing the report	• Staff training and clearly written SOP
Producing a report that is illegible	• Staff training and clearly written SOP
Failing to send the report	• Staff training and clearly written SOP

4.7 ASSESSMENT

Assessment is defined as the systematic examination of the laboratory quality management system to demonstrate that the laboratory is meeting regulatory, accreditation and customer requirements (12).

External quality assessment (EQA)
EQA is a process to objectively check the laboratory's performance of testing by an external facility (13). The methods commonly used are:

- Proficiency testing – unknown samples are sent from an external facility for testing and the results are analysed, compared and reported;
- Rechecking/retesting – slides that have been read are rechecked by an external facility; and
- Onsite evaluation.

EQA is essential, as it:

- Promotes and maintains professional standards in reporting;
- Provides individual performance appraisal based on peer review; and
- Promotes dialogue and discussion between pathologists.

Laboratories should be enrolled in an accredited EQA programme. The standard of care for cancer diagnoses in high-income countries requires a minimum of two different pathologists to review a malignant diagnosis before treatment. For low- and middle-income countries with limited staffing, telepathology and telementoring can achieve this level of review.

Audits
Audits allow the laboratory to understand how well it is performing when compared to a benchmark or standard. During assessment, information is gathered about:

- Processes and operating procedures
- Staff competence and training
- Equipment
- Environment
- Handling of samples
- Quality control and verification of results
- Recording and reporting practices.

Any identified problems or deviation from the standard should be reviewed for its root cause and corrective action should be taken to improve processes and procedures. Both internal and external audits yield useful information.

Internal audit
An internal audit is conducted by each laboratory and could be performed as frequently as needed for continuous improvement and maintenance of the laboratory quality system (16). It could help the laboratory to increase staff awareness of quality system requirements, understand where preventive or corrective action is needed and prepare for an external audit.

External audit
An external audit is conducted by agencies from outside the laboratories (e.g. health authorities, accreditation bodies) and verifies whether laboratory policies, processes and procedures are documented and comply with designated standards. Different standards could be used for the assessment processes, ranging from international standards to a locally developed checklist.

Accreditation

Accreditation is a procedure by which an authoritative body gives formal recognition that an organization is competent to carry out specific tasks according to certain standards and is recognized as delivering accurate and reproducible results (34). Accreditation of pathology laboratories is now becoming a routine in most countries (16).

Accreditation is carried out by a qualified organization and the following points are critical to comply with:

- Process control: the pathology laboratory participates in appropriate EQA programmes and runs efficient internal quality platforms.
- Document control: a written, comprehensible and applicable system of document preparation, organization and accessibility to relevant staff. Written descriptions of procedures and processes must be available.
- Personnel management: sufficient and properly qualified staff with updated job descriptions. A continuous education programme for all staff members must be implemented and monitored.
- Implementation of and compliance with health and safety measures.
- Management of facilities and equipment.
- Management of data and information: records must be supported by technical and electronic devices; data storage and retrieval must be guaranteed.
- Management of reagents, calibration and materials: written records on materials and activities must be maintained to allow full traceability.
- Specimen collection and transportation.
- Receipt of specimens: there must be appropriate space available for receiving specimens, with spatial separation from lab spaces where pathology-specific activities are performed.
- Examination procedures: all processes must be documented, verified, validated and tested for quality.
- Reporting of results: clear instructions on transmission of results, such as oral reports and e-mails.
- Monitoring and evaluation: there should be documentation of internal audits, actions undertaken following EQA results and records of unresolved matters.

Photo credit: Mohana S. Narasimhamurthy

4.8 PROCESS IMPROVEMENT

Process improvement refers to establishing a system for continual improvement in laboratory quality over time. Measuring performance is a starting point, required throughout the process of strengthening pathology laboratory service. A set of quality indicators that are objective and capable of measuring should be defined to track changes over time and ensure transparency and accountability for results. Table 12 identifies examples of some quality indicators for pathology services.

TABLE 12. SAMPLE QUALITY INDICATORS

1. SUBOPTIMAL SPECIMEN SUBMITTED FOR DIAGNOSIS

Definition	Percentage of tests that were not performed, or results are not available, due to any of the following reasons or combination thereof: inadequate container; inappropriate volume; compromised specimen; specimen contamination; improper storage or transport.
Purpose	To ensure appropriate tissue sampling.
Data collection	Data should be recorded on all specimens at the time of reception on the status of the request form, specimen, container and overall impression as follows:
	Specimen received: [ ] acceptable (1) [ ] unacceptable (0)
	Unacceptable due to: [ ] inadequate container (1) [ ] inappropriate preservation (2) [ ] insufficient specimen (3) [ ] other (4)
Data reported	The total of the acceptable score divided by the total the specimen received gives the rate (%) of pathology analysis performed. A total of each unacceptable code is provided per reporting period.
Corrective action	When a laboratory team member marks a specimen as unacceptable, the clinician submitting the specimen should be notified immediately via email, telephone or text, and the time and date of the notification should be recorded in the logbook. Corrective action with the clinical team may include providing training on proper specimen collection and handling.

2. TURNAROUND TIME

A) Overall turnaround time

B) Clinical delivery time

C) Laboratory turnaround time

D) Critical value turnaround time

Definition	Time interval of tests recorded: **A)** from specimen collected until results verified **B)** from specimen collected until specimen received in the laboratory **C)** from specimen received until results verified **D)** from results are verified until the critical value is reported via phone or text
Purpose	To measure timeliness of pathology service
Data collection and report	For all of these measures, dates and times must be recorded for specimens on the request form or logbook; or can be automatically collected in computerized laboratory information systems (LIS). The reportable intervals are shown below:

Time stamp	Recorded by	Recorded in	Intervals affected
Specimen collected	Clinician	Requisition form	**A, B**
Specimen received	Technician	Log book/LIS	**B, C**
Specimen reported	Pathologist	Log book/LIS	**A, B, D**
Clinician notified of critical value	Pathologist	Log book/LIS	**D**

Data reported	These values are reported in aggregate and could be parsed by day, week, month, pathologist, technical staff, clinician, etc. if they are inordinately long in order to determine corrective action.
Corrective action	Depending on the turnaround time interval affected, an investigation is needed to create corrective action plans. The supervisory laboratory should have goals for all of these intervals so that comparison with the standard is done by each reporting period. Measurement of these intervals for a newly assessed laboratory for a run-up period may be needed to set real-time realistic goals for these intervals.

3. OVERALL DISCREPANCY RATE IN DIAGNOSIS

Definition	Rate of discrepancies (major and minor) per overall cases by comparing the results of the external review to the results of the primary review.
Purpose	To measure accuracy of pathology diagnosis.
Data collection	Multiple laboratories within a system, country or region could be aggregated into a collective external quality control group for determination of diagnostic accuracy for the laboratory. In this setting, collections of validated cases are used by the supervisory laboratory to "test" each laboratory in the system for its agreement or disagreement with the established diagnosis. At a minimum, evaluation should be done quarterly and from one to three cases per time period.
Data reported	The rate of overall discrepancies is reported as a percentage (%) of total cases reviewed.
Corrective action	All malignant diagnosis discrepancies should be immediately followed up with pathologists with reference material/explanatory material to demonstrate the correct diagnosis and any teaching points or pearls.

Source: Adapted from American Society for Clinical Pathology (35).

4.9 CUSTOMER SERVICE

Customers of a pathology laboratory are patients, physicians, other health-care providers, public health agencies and the community. It is important to remember that meeting customer needs is the primary goal of a laboratory, not only the technical competency. Customer satisfaction could be sought using:

- Monitoring quality indicators
- Internal audit
- Management review
- Satisfaction surveys
- Interviews and focus groups.

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ANNEXES

ANNEX 1. PREPARATION OF 10% NEUTRAL BUFFERED FORMALIN (NBF) FROM STOCK SOLUTIONS

The standard stock solution of formalin is typically 37% formaldehyde in aqueous solution and unbuffered. To make a histological fixative (10% NBF) from this, a 10% solution of the stock formalin is needed (i.e. one part of the stock formalin with nine parts water). This makes an unbuffered formalin solution, which will have a pH of 3–4. If used unbuffered, then the acidity can react with haemoglobin in the tissues to produce dark brown acid formaldehyde haematin precipitates, which complicate histological interpretation.

To adjust the 10% formalin solution to a neutral pH (6.8–7.2), it must be mixed in quantities of a buffer, typically sodium phosphate. A recommended recipe is as follows:

- 37% formaldehyde (stock solution) 100 ml
- distilled water 900 ml
- sodium phosphate, dibasic (Na_2HPO_4) 6.5 g
- sodium phosphate, monobasic (NaH_2PO_4) 4 g

The prepared 10% NBF must be kept at room temperature for 24 hours before use.

Source: Adapted from University of Surrey (36).

ANNEX 2. SAMPLE HISTOPATHOLOGY REQUEST FORM

Patient details

Patient ID No.:

Given name:

Surname:

Date of birth: Sex:

Address:

For laboratory use only

Accession No.

Signature:

Received date and time:

Submitting service

Name of hospital/department:

Contact number:

Name of physician:

Report required: ☐ Today ☐ Within 24h In ____ weeks

Specimen details

Tissue/site	Date and time of collection	Procedure
1.		
2.		
3.		
4.		

Clinical details

Clinical diagnosis:

Clinical history:

Gross description:

Reason for pathology request:

Previous histopathology/cytology: ☐ No ☐ Yes: specimen number

ANNEX 3. SAMPLE CYTOPATHOLOGY REQUEST FORM

Patient details

Patient ID No.:

Given name:

Surname:

Date of birth: Sex:

Address:

For laboratory use only

Accession No.

Signature:

Received date and time:

Submitting service

Name of hospital/department:

Contact number:

Name of physician:

Specimen collected: Date _____ Time _____

GYN specimen

Previous cytopathology: ☐ No ☐ Yes : date _____ diagnosis _____

Source:

☐ vaginal: ☐ conventional smear (number of slides: ____) ☐ liquid-based
☐ cervical: ☐ conventional smear (number of slides: ____) ☐ liquid-based
☐ endometrial: ☐ conventional smear (number of slides: ____) ☐ liquid-based

G ____ P ____ LMP _____ or post-menopausal

☐ pregnant ☐ postpartum ☐ post-menopausal bleeding
☐ birth control pills ☐ IUD present ☐ hormone therapy ☐ irradiation therapy

Other clinical information

Non-GYN specimen

Previous cytopathology: ☐ No ☐ Yes : date _____ diagnosis _____

Source:

☐ bronchial wash ☐ bronchial wash ☐ urine voided ☐ urine catheterized
☐ bladder wash ☐ breast secretion ☐ peritoneal fluid ☐ pericardial fluid
☐ cerebrospinal fluid ☐ sputum ☐ fine needle aspiration:
☐ other:

Clinical information

ANNEX 4. IMMUNOHISTOCHEMICAL STAINING COMMONLY USED IN CANCER MANAGEMENT

IHC requires a primary antibody ("test"), secondary antibodies, and a detector to demonstrate the presence of a given molecule (typically a protein) in a tissue section. The process can be done manually (adding one reagent at a time by hand) or in an automated fashion using pre-made kits and robotic equipment. The fiscal cost of IHC is roughly equivalent between manual and automated processes; therefore, the determination of approach is based on volume of samples the laboratory receives and personnel.

	STAIN	PURPOSE	EXAMPLES OF USE IN CANCER MANAGEMENT
For solid tumours			
	Oestrogen receptor (ER)	Prognostic/predictive	Breast cancer
	Progesterone receptor (PgR)	Prognostic/predictive	Breast cancer
	HER-2	Prognostic/predictive	Breast cancer
	Leucocyte common antigen (CD45)	Marker of haematopoietic cells	Lymphoma
	Pan-cytokeratin (AE1/AE3)	Marker of epithelial differentiation	Carcinoma vs sarcoma
	Desmin	Marker of myogenic origin	Rhabdomyosarcoma
	Myogenin	Marker of myogenic origin	Rhabdomyosarcoma
	Synaptophysin	Marker of neuroendocrine differentiation	Neuroendocrine neoplasm
	S100	Marker for neural tissue and melanoma	Melanoma; nerve sheath tumours
For haematological malignancies			
	Ki-67 (Mib1)	Cellular proliferation (all cancers)	Lymphoma; neuroendocrine neoplasms
	CD3	T- lymphocyte marker	Adult T cell leukaemia/ lymphoma
	CD5	Lymphocyte marker	Mantle cell lymphoma
	CD10	Lymphocyte marker	Acute lymphoblastic leukamia
	CD15	Detection of the sialyl Lewis X	Hodgkin lymphoma
	CD20	Prognostic/ predictive	Follicular lymphoma
	CD23	Surface marker for lymphoma	Chronic lymphocytic leukaemia
	CD30	Surface marker for lymphoma	Anaplastic large cell lymphoma
	CD79a	B- lymphocyte marker	Multiple myeloma
	BCL2	B- lymphocyte marker	Follicular lymphoma
	BCL6	B- lymphocyte marker	Burkitt lymphoma
	MYC	Prognostic/diagnostic	Burkitt lymphoma
	IRF/ MUM1	B- lymphocyte marker	Diffuse large B-cell lymphoma
	Cyclin D1	Prognostic marker	Mantle cell lymphoma 7
	Terminal deoxynucleotidyl transferase (TdT)	Immature lymphocyte marker	Acute lymphoblastic leukaemia

Sources: WHO 2017 (3); WHO 2019 (14).

ANNEX 5. SAMPLE PATHOLOGY SYNOPTIC REPORTING FORM

Carcinoma of the Cervix
Histopathology Reporting Guide

Family/Last name ____ Date of birth DD – MM – YYYY

Given name(s) ____

Patient identifiers ____ Date of request DD – MM – YYYY Accession/Laboratory number ____

Elements in **black text** are CORE. Elements in grey text are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

PRIOR TREATMENT

Previous procedure performed

- ◯ Loop
- ◯ Cone
- ◯ Trachelectomy (simple or radical)
- ◯ Other, *specify*
- ◯ Information not provided
- ◯ No prior procedure

Previous therapy

- ◯ Chemotherapy
- ◯ Radiation
- ◯ Chemoradiation
- ◯ Other, *specify*
- ◯ Information not provided
- ◯ No prior therapy

SPECIMENS SUBMITTED (select all that apply)

- ☐ Loop excision*
  - ◯ Not specified
- ☐ Cone biopsy
- ☐ Trachelectomy
  - ◯ Simple
  - ◯ Radical
  - ◯ Type not specified
- ☐ Hysterectomy
  - ◯ Simple
  - ◯ Radical
  - ◯ Part of exenteration
  - ◯ Type not specified
- ☐ Left tube
- ☐ Right tube
- ☐ Left ovary
- ☐ Right ovary
- ☐ Left parametrium
- ☐ Right parametrium
- ☐ Vaginal cuff
- ☐ Pelvic exenteration
  - ☐ Urinary bladder
  - ☐ Rectum
  - ☐ Vagina
  - ☐ Sigmoid colon
  - ☐ Other, *specify*
- ☐ Lymphadenectomy specimen(s)
  - ☐ Sentinel node(s)
    - ☐ Left
    - ☐ Right
  - ☐ Regional nodes: pelvic
    - ☐ Left
    - ☐ Right
  - ☐ Regional nodes: para-aortic
  - ☐ Non-regional nodes: inguinal
    - ☐ Left
    - ☐ Right
  - ☐ Other node group, *specify*
- ☐ Other, *specify*

* *Loop excision includes – loop electrosurgical excision procedure (LEEP and large loop excision of the transformation zone (LLETZ).*

SPECIMEN DIMENSIONS

Number of tissue pieces**

Tissue piece dimensions** *(Note: Record for each piece)*

mm	x	mm	x	mm	
mm	x	mm	x	mm	
mm	x	mm	x	mm	

Cervix***

DIAMETER OF ECTOCERVIX mm x mm

DEPTH OF SPECIMEN mm

Vaginal cuff****

- ◯ Not applicable

MINIMUM LENGTH mm

MAXIMUM LENGTH mm

Left parametrium

- ◯ Not applicable

LATERAL EXTENT mm

Right parametrium

- ◯ Not applicable

LATERAL EXTENT mm

** *Applicable to loop/cone biopsies only.*
*** *Applicable to loop/cone biopsies and trachelectomy specimens only.*
**** *Applicable to trachelectomy and hysterectomy specimens.*

MACROSCOPIC APPEARANCE OF TUMOUR(S)

- ◯ No macroscopically visible tumour
- ☐ Exophytic/polypoid
- ☐ Flat
- ☐ Ulcerated
- ☐ Circumferential/barrel shaped cervix
- ☐ Other, *specify*

Source: International Collaboration on Cancer Reporting, 2019. Templates for synoptic reporting of various cancer types are available for free download from http://www.iccr-cancer.org/datasets

MACROSCOPIC TUMOUR SITE(S) (select all that apply)

- ◯ No macroscopically visible tumour
- ◯ Indeterminate
- ☐ Ectocervix
  - ☐ Anterior
  - ☐ Posterior
  - ☐ Left lateral
  - ☐ Right lateral
  - ☐ Circumference of cervix
- ☐ Endocervix
  - ☐ Anterior
  - ☐ Posterior
  - ☐ Left lateral
  - ☐ Right lateral
  - ☐ Circumference of cervix
- ☐ Vagina
- ☐ Uterus
  - ☐ Lower uterine segment
  - ☐ Corpus
- ☐ Parametrium
  - ☐ Left
  - ☐ Right
- ☐ Other organs or tissues, *specify*

BLOCK IDENTIFICATION KEY

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

TUMOUR DIMENSIONS

(If separate tumours specify the dimensions for each tumour)

◯ Tumour dimensions cannot be determined

Horizontal extent mm x mm At least#

Depth of invasion mm At least#

OR ◯ Not assessable

If not assessable record:

Thickness mm

 # It is advisable to include "at least" for the tumour measurements in loop or cone excisions when tumour is present at a resection margin/s. If not applicable, delete "at least".

HISTOLOGICAL TUMOUR TYPE

HISTOLOGICAL TUMOUR GRADE

- ◯ Not graded/applicable
- ◯ G1: Well differentiated
- ◯ G2: Moderately differentiated
- ◯ G3: Poorly differentiated
- ◯ GX: Cannot be graded

LYMPHOVASCULAR INVASION

◯ Not identified ◯ Indeterminate ◯ Present

COEXISTENT PATHOLOGY

(*Required for loop/cone excisions/trachelectomies only and recommended for other specimens)*

Squamous intraepithelial lesion (SIL) (CIN)

- ◯ Not identified
- ◯ Present

⇩

GRADE

- ◯ Low-grade SIL (LSIL) (CIN 1)
- ◯ High-grade SIL (HSIL) (CIN 2/3)

Adenocarcinoma in-situ (AIS)/High-grade cervical glandular intraepithelial neoplasia (HG CGIN)

- ◯ Not identified
- ◯ Present

Stratified mucin-producing intraepithelial lesion (SMILE)

- ◯ Not identified
- ◯ Present

Other possible precursor lesions

- ◯ Not identified
- ◯ Present
  - ☐ Lobular endocervical glandular hyperplasia
  - ☐ Adenocarcinoma in situ of gastric type
  - ☐ Other, *specify*

EXTENT OF INVASION

◯ Not applicable

Vagina

◯ Not involved ◯ Not applicable

◯ Involved

- ☐ Upper two thirds
- ☐ Lower third

Lower uterine segment

◯ Not involved ◯ Not applicable

◯ Involved

Endometrium

◯ Not involved ◯ Not applicable

◯ Involved

Myometrium

◯ Not involved ◯ Not applicable

◯ Involved

Parametrium

◯ Not involved ◯ Not applicable

◯ Involved

- ☐ Left
- ☐ Right

Fallopian tube

◯ Not involved ◯ Not applicable

◯ Involved

- ☐ Left
- ☐ Right

Ovary

◯ Not involved ◯ Not applicable
◯ Involved
☐ Left
☐ Right

Bladder

◯ Not involved ◯ Not applicable
◯ Involved, *specify compartment*

Rectum

◯ Not involved ◯ Not applicable
◯ Involved, *specify compartment*

Other organs or tissues

◯ Not involved ◯ Not applicable
◯ Involved, *specify*

PATHOLOGICALLY CONFIRMED DISTANT METASTASES

◯ Not identified
◯ Present, *specify site(s)*

ANCILLARY STUDIES

◯ Performed ◯ Not performed

HPV testing, *specify details*

Immunohistochemistry, *specify details*

Other, *specify details*

MARGIN STATUS

For carcinoma

HYSTERECTOMY/TRACHELECTOMY SPECIMEN

Margin	Involved	Not involved	Distance from tumour (mm)	Cannot be assessed
Ectocervical/vaginal cuff				
Endocervical ^				
Radial/deep stromal				
Closest lateral	◯ Left ◯ Right			

LOOP/CONE

Margin	Involved	Not involved	Distance from tumour (mm)	Cannot be assessed
Ectocervical				
Endocervical				
Radial/deep stromal				
Unspecified ^^				

For preinvasive disease

Margin	HSIL				AIS				SMILE				Margin is not applicable to specimen
	Involved	Not involved	Dist. from margin (mm)	Cannot be assessed	Involved	Not involved	Dist. from margin (mm)	Cannot be assessed	Involved	Not involved	Dist. from margin (mm)	Cannot be assessed	
Ectocervical/vaginal cuff													
Endocervical													
Radial/deep stromal													
Unspecified ^^													

^ *This is required only for trachelectomy specimens.*
^^ *Use for loop/cone biopsies where it is not possible to say whether the margin is ectocervical or endocervical.*

LYMPH NODE STATUS

◯ Not submitted

^^^ *If the actual number of lymph nodes examined or the number of positive nodes cannot be determined due, for example, to fragmentation, then this should be indicated in the response.*

Lymph Node Type	Detail	Number of lymph nodes examined ^^^	Number of positive lymph nodes ^^^
Sentinel node(s)	Left		
	Right		
Regional nodes: pelvic	Left		
	Right		
Regional nodes: para-aortic			
Non-regional nodes: inguinal	Left		
	Right		
Other node group, *specify*			

PROVISIONAL PATHOLOGICAL STAGING PRE-MDTM

FIGO (2018 edition) (Reproduced with permission)

Stage I:The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- ◯ IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
  - ◯ IA1 Measured stromal invasion <3 mm in depth
  - ◯ IA2 Measured stromal invasion ≥3 mm and <5 mm in depth
- ◯ IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
  - ◯ IB1 Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - ◯ IB2 Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - ◯ IB3 Invasive carcinoma ≥4 cm in greatest dimension

Stage II: The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

- ◯ IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - ◯ IIA1 Invasive carcinoma <4 cm in greatest dimension
  - ◯ IIA2 Invasive carcinoma ≥4 cm in greatest dimension
- ◯ IIB With parametrial involvement but not up to the pelvic wall

Stage III: The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes[c]

- ◯ IIIA Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
- ◯ IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- ◯ IIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
  - ◯ IIIC1 Pelvic lymph node metastasis only
  - ◯ IIIC2 Paraaortic lymph node metastasis

Stage IV: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV

- ◯ IVA Spread of the growth to adjacent organs
- ◯ IVB Spread to distant organs

[a] *Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.*

[b] *The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.*

[c] *Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIc1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.*

TNM STAGING (UICC TNM 8th edition 2016)[##]

TNM Descriptors

☐ m - multiple primary tumors ☐ r - recurrent
☐ y - post-therapy

Primary tumour (pT)

- ◯ TX Primary tumour can not be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ (preinvasive carcinoma)
- ◯ T1[1] Tumour confined to the cervix
  - ◯ T1a[2,3] Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[4]
  - ◯ T1a1 Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
  - ◯ T1a2 Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
  - ◯ T1b Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
  - ◯ T1b1 Clinically visible lesion 4.0 cm or less in greatest dimension
  - ◯ T1b2 Clinically visible lesion more than 4.0 cm in greatest dimension
- ◯ T2 Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
  - ◯ T2a Tumour without parametrial invasion
  - ◯ T2a1 Clinically visible lesion 4.0 cm or less in greatest dimension
  - ◯ T2a2 Clinically visible lesion more than 4.0 cm in greatest dimension
  - ◯ T2b Tumour with parametrial invasion
- ◯ T3 Tumour extends to pelvic wall, involves lower third of vagina, causes hydronephrosis or nonfunctional kidney
  - ◯ T3a Tumour involves lower third of vagina
  - ◯ T3b Tumour extends to pelvic wall, causes hydronephrosis or nonfunctional kidney
- ◯ T4 Tumour invades mucosa of bladder or rectum or extends beyond true pelvis[5]

[1] *Extension to the corpus uteri should be disregarded.*

[2] *The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion.*

[3] *All macroscopically visible lesions even with superficial invasion are T1b/IB.*

[4] *Vascular space involvement, venous or lymphatic, does not affect classification.*

[5] *Bullous oedema is not sufficient to classify a tumour as T4.*

Regional lymph nodes(pN)

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley-Blackwell.

ANNEX 6. SAMPLE QUESTIONNAIRE FOR ASSESSMENT OF PATHOLOGY SERVICES AT THE FACILITY LEVEL

A GENERAL INFORMATION

1	Name of the laboratory	
2	Address	
3	Telephone	
4	E-mail	
5	Name of the laboratory director	
6	Date of the assessment	
7	Name of the assessor/s	
8	Contact details of the assessor/s	
9	Name of the responding person/s	
10	Level of laboratory	☐ National referral ☐ Regional ☐ District ☐ Primary
11	What are the days of operation of routine service?	
12	On average, how many hours per day does the facility provide service?	

B PHYSICAL INFRASTRUCTURE

1	Does the management provide a safe and adequate working space and environment?	☐ Yes ☐ No
2	Is there an effective separation between adjacent laboratory sections in which there are incompatible activities?	☐ Yes ☐ No
3	Are work areas clean and well maintained?	☐ Yes ☐ No
4	Does this laboratory have appropriate ventilation with adequate humidity and temperature conditions?	☐ Yes ☐ No
5	Is specific ventilation installed in areas where biohazardous materials (e.g. formalin) are being handled?	☐ Yes ☐ No
6	Does the laboratory face electricity interruption?	☐ Never ☐ Sometimes ☐ Regularly
7	Other than the primary source, does the laboratory have a secondary or back-up source of electricity?	☐ Yes ☐ No
8	Does the laboratory face water shortages?	☐ Never ☐ Sometimes ☐ Regularly
9	Are written biosafety procedures available?	☐ Yes ☐ No
10	Are all staff provided with appropriate personal protective equipment (PPE)?	☐ Yes ☐ No
11	Does this facility have a functioning telephone that is available to call outside during normal working hours?	☐ Yes ☐ No
12	Does this facility have a functioning computer with internet access?	☐ Yes ☐ No

C EQUIPMENT

1	Does the management provide essential equipment and ensure its functionality?	☐ Yes ☐ No
2	Is there an adequate budget assigned for equipment purchase/maintenance?	☐ Yes ☐ No
3	Is there a dedicated person in charge of the equipment (maintenance management, etc.)?	☐ Yes ☐ No
4	Is there an equipment inventory with identification number?	☐ Yes ☐ No
5	Is the equipment purchased from suppliers who can provide maintenance, servicing and spare parts for the equipment?	☐ Yes ☐ No

6	Are all staff duly trained and authorized before first using equipment?	☐ Yes ☐ No
7	Are there user manuals for the equipment in the language commonly used by the staff?	☐ Yes ☐ No
8	Is a preventive maintenance programme in place?	☐ Yes ☐ No
9	Is there a documented procedure for the decommissioning of redundant or non-functional equipment?	☐ Yes ☐ No

D SUPPLIES AND REAGENTS

1	Does the management provide adequate supplies to ensure continuity of service?	☐ Yes ☐ No
2	Is there an adequate budget assigned for supplies and reagent purchase?	☐ Yes ☐ No
3	Are there responsible staff for consumable and reagent management (inventory, order, etc.)?	☐ Yes ☐ No
4	Is there an effective inventory management system in place to avoid stockouts?	☐ Yes ☐ No
5	Is the date of opening clearly written on the reagents/kits?	☐ Yes ☐ No
6	Is there adequate storage to ensure that all supplies are kept at optimal conditions?	☐ Yes ☐ No
7	Are disposable supplies (e.g. tips, plastic pipettes, gloves) reused?	☐ Never ☐ Sometimes ☐ Regularly
8	Are expired reagents used?	☐ Never ☐ Sometimes ☐ Regularly
8.1	If sometimes or regularly, is quality control performed on these expired reagents?	☐ Yes ☐ No

E HUMAN RESOURCES

1	Is there a laboratory organizational chart that describes the management and supervisory arrangements?	☐ Yes ☐ No
2	How many of the following staff do you have in this laboratory?	
2.1	Trained pathologist in cancer diagnosis: • adult cancer • haematological cancer • childhood cancer	
2.2	Biomedical laboratory scientist trained in handling: • histopathology specimens • cytopathology specimens	
2.3	Biomedical engineer	
2.4	Clerical support worker/administrative staff	
3	Are job descriptions defining qualifications and duties available?	☐ Yes ☐ No
4	Is the budget for staff salaries adequate for the need?	☐ Yes ☐ No
5	Is there an adequate budget assigned for staff education?	☐ Yes ☐ No
6	Is there a professional development programme in place for the staff?	☐ Yes ☐ No
7	Is continuing education (training, workshop, conference, etc.) provided to staff members?	☐ Yes ☐ No

F SPECIMEN MANAGEMENT

1	**Pre-analytical phase**	
1.1	Are standard operating procedures (SOPs) for collection and fixation of specimens available for those requesting tests?	☐ Yes ☐ No
1.2	Is a standard pathology request form available for those requesting tests?	☐ Yes ☐ No
1.3	Does the laboratory receive specimens or isolates from other laboratories?	☐ Yes ☐ No
1.4	Does the laboratory refer specimens or isolates to other laboratories?	☐ Yes ☐ No
1.5	Are there SOPs in accordance with International Air Transport Association (IATA) regulations for the packing and shipping of samples to other laboratories?	☐ Yes ☐ No
2	**Analytical phase**	
2.1	Is there a written policy to deal with incorrectly identified or incorrect specimens received in the laboratory?	☐ Yes ☐ No
2.2	Is each sample given a unique accession number along with the date and time of receipt?	☐ Yes ☐ No
2.3	Are there SOPs for specimen handling and processing available in the laboratory?	☐ Yes ☐ No

3	**Post-analytical phase**	
3.1	Are results reported and recorded in a standardized format?	☐ Yes ☐ No
3.2	Are the results reviewed and authorized before the results are released?	☐ Yes ☐ No
3.3	Is there an immediate notification of physicians when results are critical for patient care?	☐ Yes ☐ No
3.4	Is there adequate storage space available for all archived patient data and reports?	☐ Yes ☐ No
3.5	Is biomedical waste disposal handled according to guidelines?	☐ Yes ☐ No
3.6	Are SOPs available for management of spills and are staff trained?	☐ Yes ☐ No

G QUALITY MANAGEMENT

1	Is there an effective and documented quality management system in place?	☐ Yes ☐ No
2	Are there responsible staff for quality management?	☐ Yes ☐ No
3	Are laboratory procedures reviewed at least annually and any necessary amendments incorporated?	☐ Yes ☐ No
4	Is there a system in place to organize the management of laboratory documents and records?	☐ Yes ☐ No
5	Does the laboratory have an internal audit programme?	☐ Yes ☐ No
6	Has the laboratory undergone an external audit by a third party within the last two years?	☐ Yes ☐ No
7	Does the laboratory hold any form of accreditation?	☐ Yes ☐ No

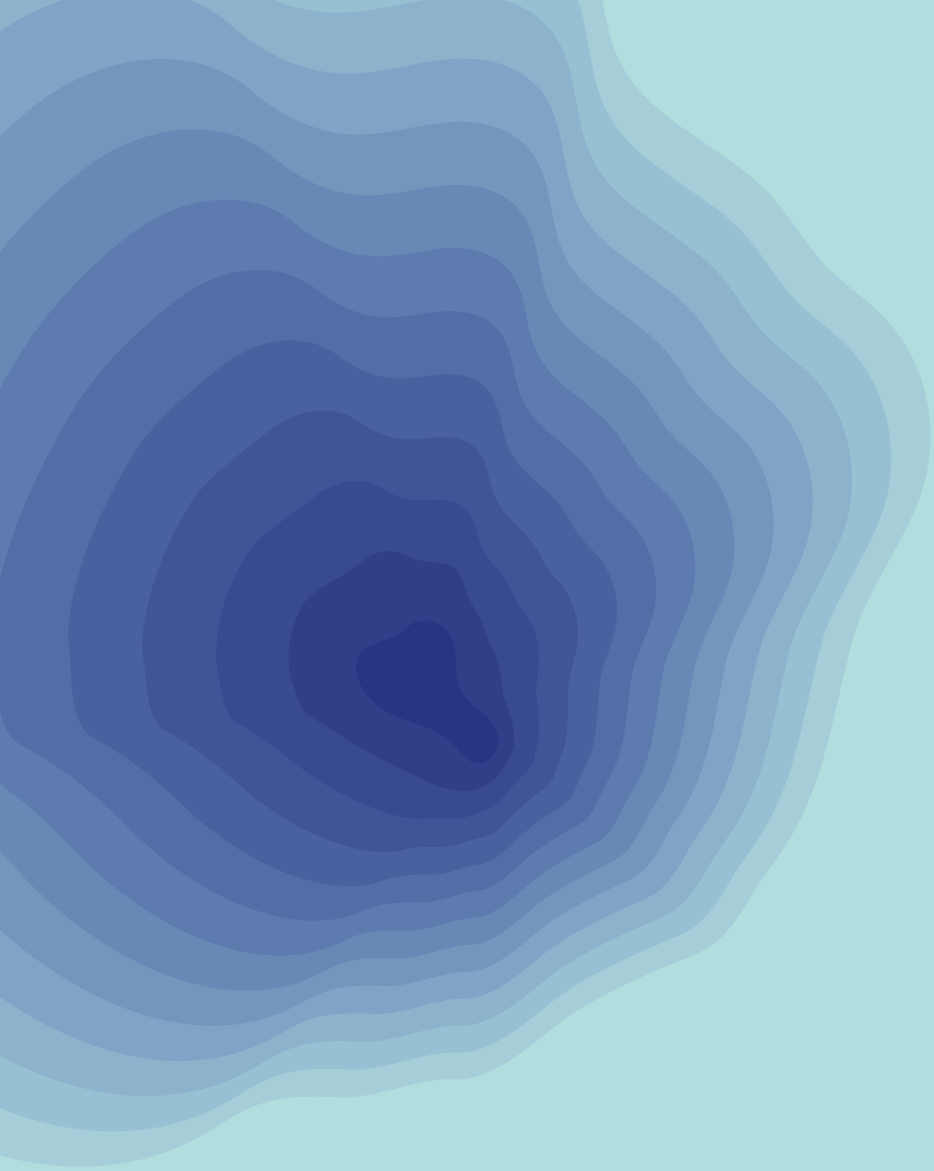
Sources: WHO 2012 (18); WHO 2015 (37).

ANNEX 7. CRITERIA FOR EVALUATING EQUIPMENT DONATION OFFERS

INDICATORS OF SUITABILITY	CRITERIA
Appropriate to setting	**Desired characteristics:** • Suitable for the level of facility and service provided • Acceptable to staff and patients • Suitable for operator skills available • Suitable for the local maintenance support capabilities • Compatible with existing equipment and consumable supplies • Compatible with existing utilities and energy supplies • Suited to the local climate, geography and conditions • Able to be run economically with local resources
Assured quality and safety	**Desired characteristics:** • Of sufficient quality to meet requirements and last a reasonable length of time • Made of durable materials • Made from material that can be easily cleaned, disinfected or sterilized without rusting • Manufactured to meet internationally recognized safety and performance standards • Suitably packaged and labelled so that it is not damaged in transit or during storage • Provided by reputable, reliable, licensed manufacturers, or registered suppliers
Affordable and cost effective	**Desired characteristics:** • Available at a price that is cost effective; quality and cost often go together (e.g. The cheaper option may be of poor quality and ultimately may prove to be costlier in the long term) • Affordable in terms of costs for freight, insurance, import tax, etc. • Affordable in terms of installation, commissioning and training of staff to use and maintain • Affordable to operate (costs of consumables, accessories and spare parts over its lifetime) • Affordable to maintain and service • Affordable to dispose of safely • Affordable in terms of the procurement process (e.g. The cost of a procurement agent or foreign exchange) • Affordable in terms of staffing costs (e.g. Costs of any additional staff or specialized training required)

INDICATORS OF SUITABILITY	CRITERIA
Ease of use and maintenance	**Equipment selected/accepted if:** • The donation solicitor has the necessary skills in terms of operating, cleaning and maintenance • Instructions and manuals are available in the proper language • User training is offered by the supplier or donor • Local after-sales support is available with proven technical skills • The possibility of additional technical assistance through service contracts exists • The equipment comes, preferably, with a warranty covering a reasonable length of time, for which the terms are well understood (e.g. Does it cover parts, labour, travel, refunds or replacements?) • A supply channel exists for equipment-related supplies (e.g. Consumables, accessories, spare parts) • There is assured availability of needed supplies for a reasonable period (up to 10 years)
Conforms to donor solicitor's policies, plans and guidelines	**Equipment accepted/selected if it conforms with:** • Purchasing and donations policy • Standardization policy • The technology level described in standard equipment lists and generic equipment specifications • Conclusions resulting from review of literature and comparative products • Conclusions resulting from feedback regarding previous purchases and donations

Source: WHO 2011 (23).



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