Technical Specification

ISO/TS 23824

First edition
2024-05

Medical laboratories — Guidance on application of ISO 15189 in anatomic pathology

Laboratoires médicaux — Recommandations pour l'application de l'ISO 15189 en anatomopathologie

Reference number
ISO/TS 23824:2024(en)

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Published in Switzerland

Contents

Page

Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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This document was prepared by Technical Committee ISO/TC 212, *Medical laboratories and in vitro diagnostic systems*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Anatomic pathology (AP) is the branch of medicine that examines tissue samples and cells by microscopy and other methods. AP seeks to answer clinical questions (e.g. Is it neoplastic? Is it malignant? Where does it arise? How can it be treated?) by rendering a diagnosis that allows the patient's caregiver to treat the patient's condition, predict the condition's response to treatment and make a judgement about the condition's prognosis.

AP comprises three activities: examination of tissue obtained from the body by biopsy, surgery or autopsy; examining exfoliated or aspirated single cells, circulating tumour cells, or groups of cells whose architectural context is often lost; and examination of deceased persons, usually to confirm or document a cause of death, or the extent of known or previously undiagnosed conditions.

Ancillary techniques such as immunohistochemical stains, (fluorescence) in-situ hybridization studies, molecular testing and advanced genomic and proteomic studies (e.g. next-generation sequencing, mass spectrometry) have complemented or even been incorporated into AP. The arrival of image analysis tools, machine learning algorithms and artificial intelligence systems will introduce new examinations to AP laboratories with a new set of risks and opportunities (e.g. automated quality control).

AP is different from other laboratory medicine specialties such as chemistry, microbiology, or haematology in several aspects. First, samples submitted for evaluation are often solid and, in many instances, unique (i.e. if the sample is exhausted or lost, it cannot be replaced by another sample) and indivisible (i.e. a part taken from the primary sample cannot be expected to have the same properties as the primary sample). Second, the structural integrity at the macroscopic scale determines diagnostic features such as margins status or orientation. Third, the examination process almost always requires at least two separate activities, macroscopic and microscopic examination, that occur at different times. Fourth, processing the sample involves many, often unrepeatable, manual steps, that introduce several risk points along the process. Finally, the analytical examination process is interpretive, performed by humans with intra- and inter-observer variability, and with no universally accepted biological reference intervals.

ISO 15189, can be applied to, and encompasses AP. This document provides guidance for AP laboratories on how the requirements contained in ISO 15189 can be met. Like ISO 15189, this document applies to both the resource and process aspects as well as the governance and management aspects of AP. ISO 15189 defines medical laboratory as an entity performing examinations of materials derived from the human body for the purpose of providing information for a diagnosis.

In AP, examination is not synonymous with diagnosis. An examination has the objective of determining the value or characteristics of a property. The result of an examination in AP can influence, and even be the sole determinant, of a diagnosis. In many instances, however, a diagnosis rests not only on the result of the AP examination but also the clinical setting and results of other examinations (e.g. medical laboratory, imaging). Rendering a diagnosis constitutes practice of medicine. While this document must not infringe on the practice of medicine, it reminds users that the practice of AP is inseparable from the activities and requirements addressed by ISO 15189 and strives to promote the welfare of patients.

This document does not impose new or more stringent requirements than ISO 15189. Instead, this document attempts to clarify the requirements by providing examples of process actions and risks, using language and concepts familiar to the AP laboratory. The left column in each table refers to the subclauses in ISO 15189 for which guidance is offered. Not every subclause of ISO 15189 is addressed, only the subclauses for which clarification or guidance was thought to be of benefit. The tables in this document are not comprehensive lists of actions and risks. They are examples of actions and risks, and conformance with every item in these tables does not imply conformance with ISO 15189.

This document is aligned with ISO 15189 and assumes basic familiarity with central themes of ISO 15189, including process and risk management, corrective action for nonconforming work, internal auditing, and effective management reviews.

Medical laboratories — Guidance on application of ISO 15189 in anatomic pathology

1 Scope

This document provides guidance to anatomic pathology (AP) laboratories on implementing a management system to meet requirements for quality and competence of ISO 15189.

NOTE International, national, or regional regulations or requirements can also apply to specific topics covered in this document.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 15189:2022, *Medical laboratories — Requirements for quality and competence*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 15189 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
anatomic pathology
AP
branch of medicine that evaluates tissue and cellular samples

Note 1 to entry: This branch of medicine is also referred to as histopathology or cellular pathology.

3.2
cytopathology
subspecialty of *anatomic pathology* (*AP*) (3.1) that evaluates features at the cellular level

3.3
diagnosis
identification of a health or disease state

Note 1 to entry: A diagnosis can be based on examination results and the disease state's signs or symptoms. A diagnosis typically classifies the disease state into separate and distinct categories or subclasses that allow medical decisions about treatment and prognosis to be made.

Note 2 to entry: Diagnosis is not synonymous with examination.

Note 3 to entry: A diagnosis is rendered by a trained, competent and authorized person. In most instances, this person is a pathologist.

3.4
examination
set of operations having the objective of determining the numerical value, text value or characteristics of a property

Note 1 to entry: An examination may be the total of a number of activities, observations or measurements required to determine a value or characteristic (e.g. dissection, microscopic examination and immunohistochemical stains can be necessary to determine whether a neoplasm extends to the margin of a surgical specimen).

Note 2 to entry: Laboratory examinations that determine a numerical value of a property are called "quantitative examinations"; those that determine the characteristics of a property are called "qualitative examinations".

[SOURCE: ISO 15189:2022, 3.8, modified — Note 1 to entry has been modified; Note 3 to entry has been removed.]

3.5
frozen section
intra-operative consultation
rapid *examination* (3.4) of a tissue sample during surgery to help with intra-operative decision making

3.6
laboratory user
individual or entity requesting services of the medical laboratory

Note 1 to entry: Laboratory user can include patients, clinicians, surgeons, practitioners, requestors and other persons, laboratories or institutions that send samples for examination.

[SOURCE: ISO 15189:2022, 3.16, modified — Note 1 to entry has been modified.]

3.7
gross examination
macroscopic examination
examination (3.4) to determine and record the characteristics and features of a tissue sample, and includes dissection of a tissue sample, often performed to select samples for microscopic evaluation from a primary sample

Note 1 to entry: Features of a tissue sample can include size, weight, visual description and lesions, such as tumours.

Note 2 to entry: Gross examination includes tissue transfer of small biopsies not needing dissection due to size.

3.8
pathologist
medical doctor practicing pathology

Note 1 to entry: Pathologists include general and specialized pathologists (e.g. cytopathologist) who perform examinations, render diagnoses and provide advisory services to laboratory users.

Note 2 to entry: In some countries, settings or situations, individuals other than pathologists can perform examinations, render diagnoses and provide advisory services to laboratory users (e.g. cytotechnologists, biomedical scientists).

3.9
primary sample
specimen
discrete portion of a body fluid or tissue or other sample associated with the human body taken for *examination* (3.4), study or analysis of one or more quantities or characteristics to determine the character of the whole

Note 1 to entry: The International Medical Device Regulators Forum (IMDRF) uses the term specimen in its harmonized guidance documents to mean a sample of biological origin intended for examination by a medical laboratory.

Note 2 to entry: Sample, according to ISO 15189, refers to one or more parts taken from a primary sample. Both definitions apply to anatomic pathology (AP), but primary sample and sample are often used synonymously. Users may use the specific term, especially when that distinction is required. Using specimen instead of primary sample or sample is acceptable.

Note 3 to entry: In AP, a sample is often called a specimen and these words can be considered synonymous.

[SOURCE: ISO 15189:2022, 3.25, modified —Notes 2 and 3 to entry were added.]

4 General requirements

4.1 Anatomic pathology (AP) laboratory

An AP laboratory, like other sections of the medical laboratory, uses materials derived from the human body for the purpose of providing information for the diagnosis, management, prevention, and treatment of disease in, or assessing the health of, human beings. The AP laboratory also provides advisory services, including the interpretation of results and offering advice on further examinations and other appropriate actions.

AP operates in close association with surgeons and interventionalists who perform operations and obtain biopsy samples. Surgeons and interventionalists are technical experts who obtain tissue for diagnostic purposes, but treatment decisions are often made by other members of the healthcare team. Thus, AP has several users: the patient, the person obtaining the tissue and the person using the tissue examination results to direct treatment.

The tissue obtained from patients can be used for rendering a diagnosis and also for biomedical research. Therefore, addressing impartiality, confidentiality and patient needs in AP requires consideration of various stakeholders (Figure 1). Several interests within and outside the AP laboratory deserve attention when building the AP management system and risk management plan.

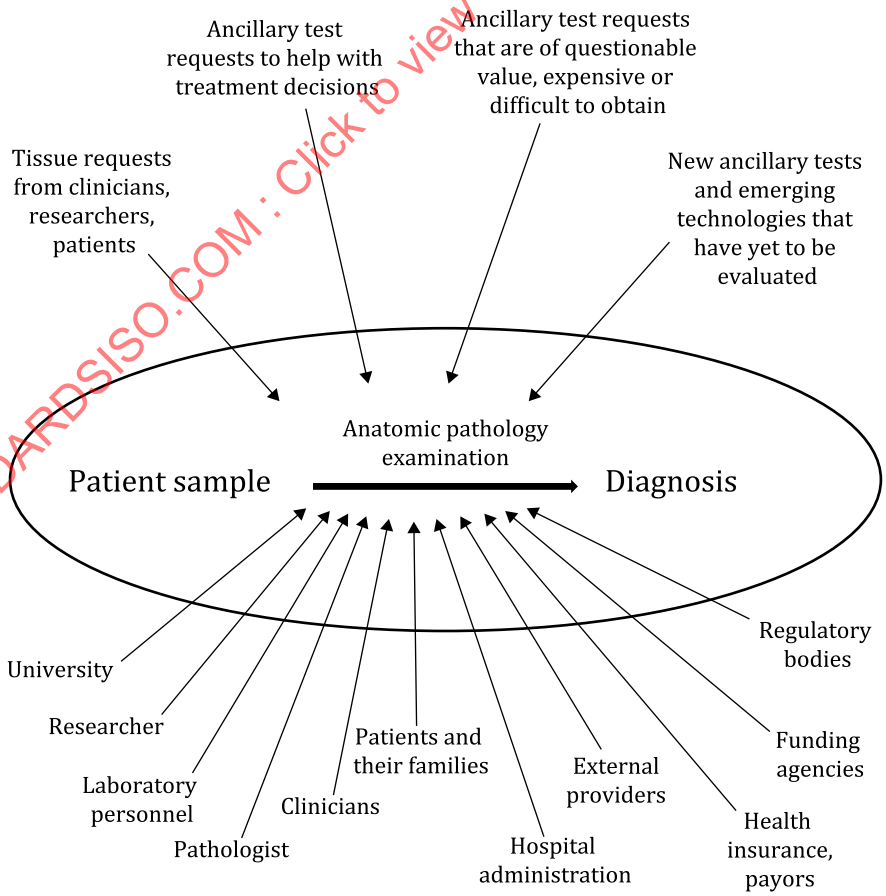

Figure 1 — Outside interests influencing anatomic pathology (AP) processes

4.2 Examples of process actions and risks for general requirements of ISO 15189

Table 1 shows examples of actions that can meet the ISO 15189:2022, Clause 4 requirements as applied to the AP laboratory's processes and also shows examples of risks in the AP laboratory for those processes.

NOTE 1 The actions and risks listed here are not comprehensive, but merely examples for guidance. Conformance with every item in Table 1 does not imply conformance with ISO 15189.

NOTE 2 ISO 22367 provides details for managing risk in medical laboratories.

Table 1 — Examples of process actions and risks for ISO 15189:2022, Clause 4

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
4.1 Impartiality	— Manage the professional and personal relationships of personnel with manufacturers and suppliers of instruments, reagents, antibodies, probes, etc. — Assess the influence of the several roles in an academic organization (e.g. research, teaching, clinical care) or across several organizations on patient care and take action to remove any conflicts of interest.	— Pathologists assuring impartiality can themselves be subject to conflicts of interest. — Research applications or methodologies that can inappropriately influence patient care. — Purchasing decisions driven by an individual instead of a group. — Financial compensation for expert witness activity that provides an incentive for one examination or diagnosis over another. — Not removing a pathologist from a case or project if impartiality is threatened.
4.2 Confidentiality	— Know the contractual arrangements that allow the laboratory to release confidential information and develop a process for when and how to notify the patient. NOTE Contractual arrangements in AP can be a formal or legal arrangement to share personal information with research organizations, insurance companies, consultants or other third parties. — Remove patient identification from samples (paraffin blocks, slides) that are used for research.	— Security of slide or tissue transport between different sites. — Potential litigation from patient or patient advocate when patient samples are used without consent. — Unintended release of patient information with research samples. — Consent not retrievable for use of materials in the future. — Cases or material taken out of the laboratory (e.g. for referral examinations or reporting at another site or at home) can lead to inadvertent breach of patient confidentiality if materials are lost or stolen.

Table 1 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
4.3 Requirements regarding patients	— Specify who is responsible for acquiring informed consent for the use of samples beyond routine laboratory examinations. — Specifically include AP in a patient's consent for research. — Establish a point of contact for patients to communicate with AP. — When reviewing examinations for appropriateness and necessity, include gross examination (e.g. sampling protocols), microscopic examinations (e.g. application of interpretive guidelines and reporting schemes), and other examinations (e.g. predictive marker or genomic testing). — Decide when it is appropriate to disclose to patients any incidents that resulted or could have resulted in patient harm. — Provide reports for patients who have died since the sample was obtained. — Share any ethical considerations with patients.	— Prioritizing AP service to the submitting physician instead of service to the patient. — Performance or selection of an examination based on cost or payment. — Obtaining referral examinations based on routines and traditions rather than what is best for the patient. — Discrimination based on patient ability to pay for examinations.

5 Structural and governance requirements

5.1 Structure of a management system

Two kinds of structures are implied in the management system requirements of ISO 15189:

a) the laboratory's organizational structure (e.g. leadership, laboratory sections);

b) the structure of the management system.

Organizational structure is often displayed graphically, such as in an organizational chart that shows people and laboratories connected by lines in a hierarchy.

Management system structure comprises mission and vision statements, policies, objectives, processes, and procedures. Laboratory management defines the goals in a set of policies. Processes transform the intent of the policies into actions for the work needed to achieve the objectives. The laboratory's stated objectives typically measure progress towards goals to achieve and are the "outcome measures" of laboratory processes and procedures. Records can provide evidence of whether processes have been implemented and are effective.

The laboratory can use two kinds of metrics. First, measuring whether the objectives were met indicates the overall success of the process, but does not detail its functionality. An objective can be met by chance with a non-functioning process or by process errors that cancel each other. Second, measuring quality indicators at different stages of the process provides information about process performance.

EXAMPLE Showing that every report includes all immunohistochemical stains performed can tell the laboratory that the objective was met. However, also showing that half the reports were revised by the pathologist to add missing stains, shows that the reporting process is flawed, and the reporting of stains is easily missed, resulting in extra work for the pathologist and introducing unnecessary risks, such as overworked pathologists and inaccurate charging.

Figure 2 shows the hierarchy and relationship between management system components.

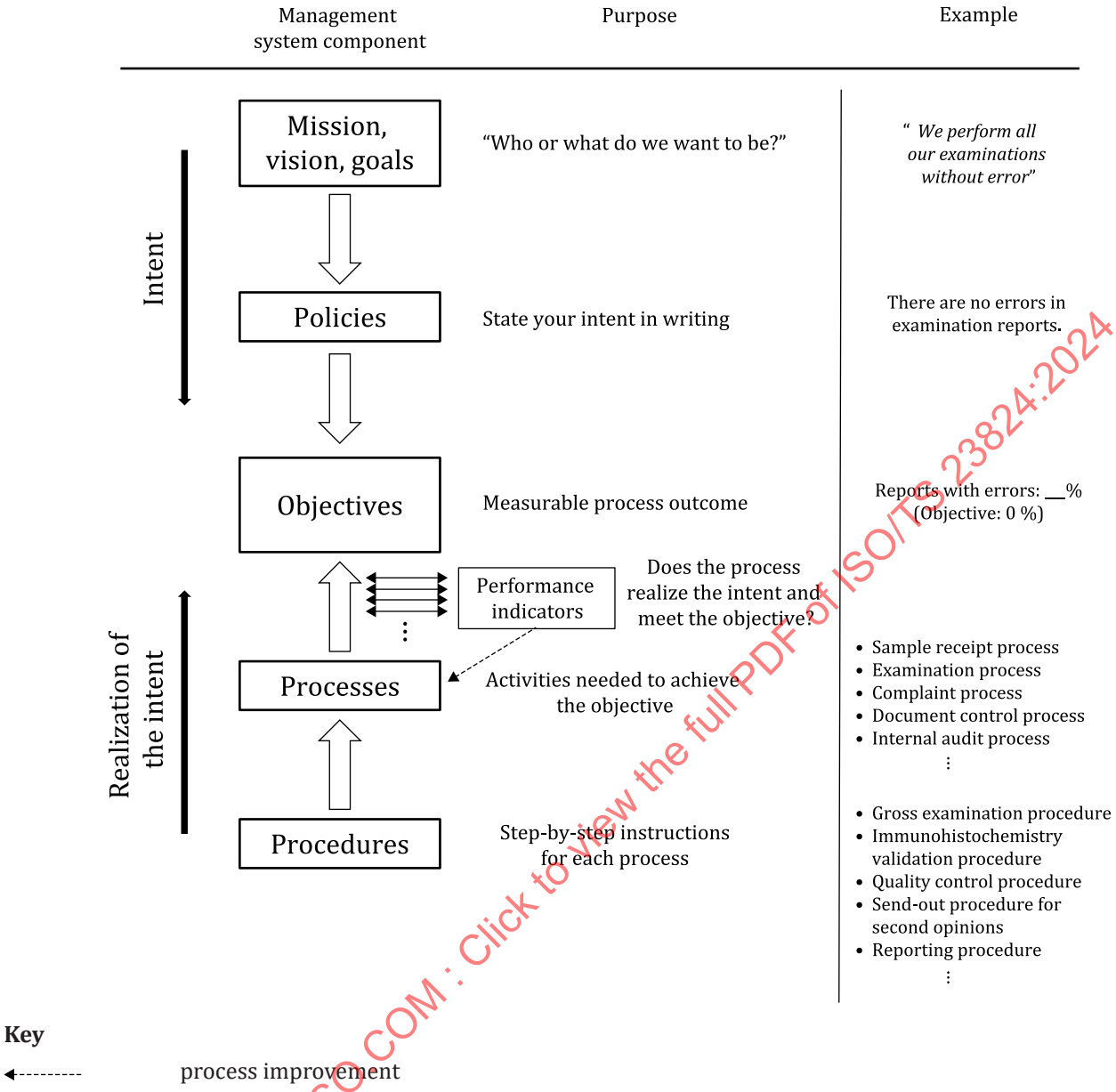

Figure 2 — Relationship of management system components

5.2 Examples of process actions and risks for structural and governance requirements of ISO 15189

Table 2 shows examples of actions that would meet the ISO 15189:2022, Clause 5 requirements as applied to the AP laboratory's processes and also shows examples of risks in the AP laboratory for those processes.

NOTE 1 The actions and risks listed here are not comprehensive, but merely examples for guidance. Conformance with every item in Table 2 does not imply conformance with ISO 15189.

NOTE 2 ISO 22367 provides details for managing risk in medical laboratories.

Table 2 — Process actions and risk examples for ISO 15189:2022, Clause 5

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
5.1 Legal entity	— Clarify legal responsibilities and liabilities, including the applicability and extent of the legal relationship of the AP laboratory with any medical laboratory or the wider organization. NOTE Specifying the intersections of AP laboratory processes with those of the hospital or wider organization in legal relationships and contracts can help delineate the activities for which the AP laboratory can be held accountable and responsible.	— Inaccurate scope stated in the AP license. — Insufficient understanding of AP legal responsibilities and liabilities.
5.2 Laboratory director	— Ensure that the person directing AP has the appropriate AP education, certification, and experience for the AP services provided. — Define who is responsible for verifying the personnel qualifications for positions in histopathology, molecular pathology, autopsy, etc. — The laboratory director may delegate the AP service to a qualified and competent person.	— A person without AP education, certification, licensure, or experience directing AP services and, therefore, potentially not understanding AP processes or AP risks, process problems, and issues. — Non-AP laboratory director managing AP personnel without proper authorization or involvement in laboratory operations.
5.3 Laboratory activities	— In the list of provided services, include not only general services (e.g. examinations, diagnosis, advising clinicians, treatment planning, test utilization) but also any specific AP specialty services (e.g. neuropathology, paediatric pathology).	— Potential AP users not aware of limitations of AP services provided. — Not being able to acquire needed advisory or interpretive AP services when timely examination, diagnosis or treatment is needed for the patient.
5.4.2 Quality management	— Document the description of the structure and management of AP services (e.g. in an organization chart).	— Separate, different, and possibly erroneous understandings of AP processes. — Quality management personnel not given the resources and authority to change processes.
5.5 Objectives and policies	— Establish who are the users of the AP laboratory: patients, physicians, researchers, screening programs, the judicial system, law enforcement, insurance companies, businesses (e.g. for pre-employment testing). — Determine how to handle requests for examinations that do not have a generally accepted intended use (e.g. immunohistochemical stains that have shown a correlation in a retrospective study but have not been evaluated in a clinical trial). — Establish rules for research on archived samples	— Inability to identify, monitor and assess trends in nonconformities that impact patient safety. — Making changes to processes or resources that affect other processes or resources that impact laboratory activities and subsequent patient care.

Table 2 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
5.6 Risk management	— Apply risk management aligned with the principles of ISO 22367. NOTE 1 The laboratory director is responsible for the application of risk management to all aspects of the laboratory operations. — Assess the risk of litigation that involves AP examinations and reports. — Mitigate risks arising from the manual nature of many AP processes, such as personnel distraction and tiredness. — Provide risk management training for all personnel. NOTE 2 The level of risk management training can vary depending on the individual's role and responsibilities. — Define when a process is deemed ineffective or improperly implemented.	— Risk management that focuses on liability and legal complaints following a nonconformity instead of proactive risk mitigation. — Lack of risk management training for all personnel who design and revise laboratory operational and management processes. — Risk management delegated to personnel unfamiliar with AP processes and practice who are unable to identify hazards or risks. — Leadership that does not emphasize the importance of risk management and does not provide leadership support for any issue that threatens effective risk management.

6 Resource requirements

6.1 Managing personnel in anatomic pathology (AP)

A feature that distinguishes AP from most other medical laboratory disciplines is that examinations are often performed by humans as opposed to instruments and can be interpretive in nature. Interpretations entail an amount of subjectivity and variability. Although it is highly desirable (and true in many cases) that all personnel performing examinations independently arrive at the same result when studying the same glass slide or digital image, this is not true in a significant subset of samples because several conditions can show overlapping macroscopic, histopathologic or cytopathologic features. Diagnoses are formulated based on examination results. Many factors affect examination results and, therefore, also diagnoses, including application and stringency of diagnostic criteria, training and experience, slide or image quality, availability of ancillary examinations, clinical history, imaging findings, pre-test probability, current workload, distractions (e.g. phone calls, frozen sections, colleague requesting consultation) and time of day (e.g. level of exhaustion, rushing to get case done).

Considerations of workload limits, work environments, resources in the form of books, internet access and other technologies, effective onboarding, allotting time for continuing education and interaction with pathologists, technical staff and other colleagues cannot be neglected. The technical staff are responsible for performing examinations correctly and competently in order to enable the pathologist to render and report the correct diagnosis for each patient. This can only be achieved with high reliability and low risk in the proper AP environment.

Figure 3 shows a generic example of how processes and procedures for personnel relate to policies.

NOTE Interpretive examination by a human is not unique to AP but is a feature of all branches of medicine and is used in other areas of the medical laboratory (e.g. sediment examination in urinalysis, blood smear examination in haematology, fungal morphology in microbiology).

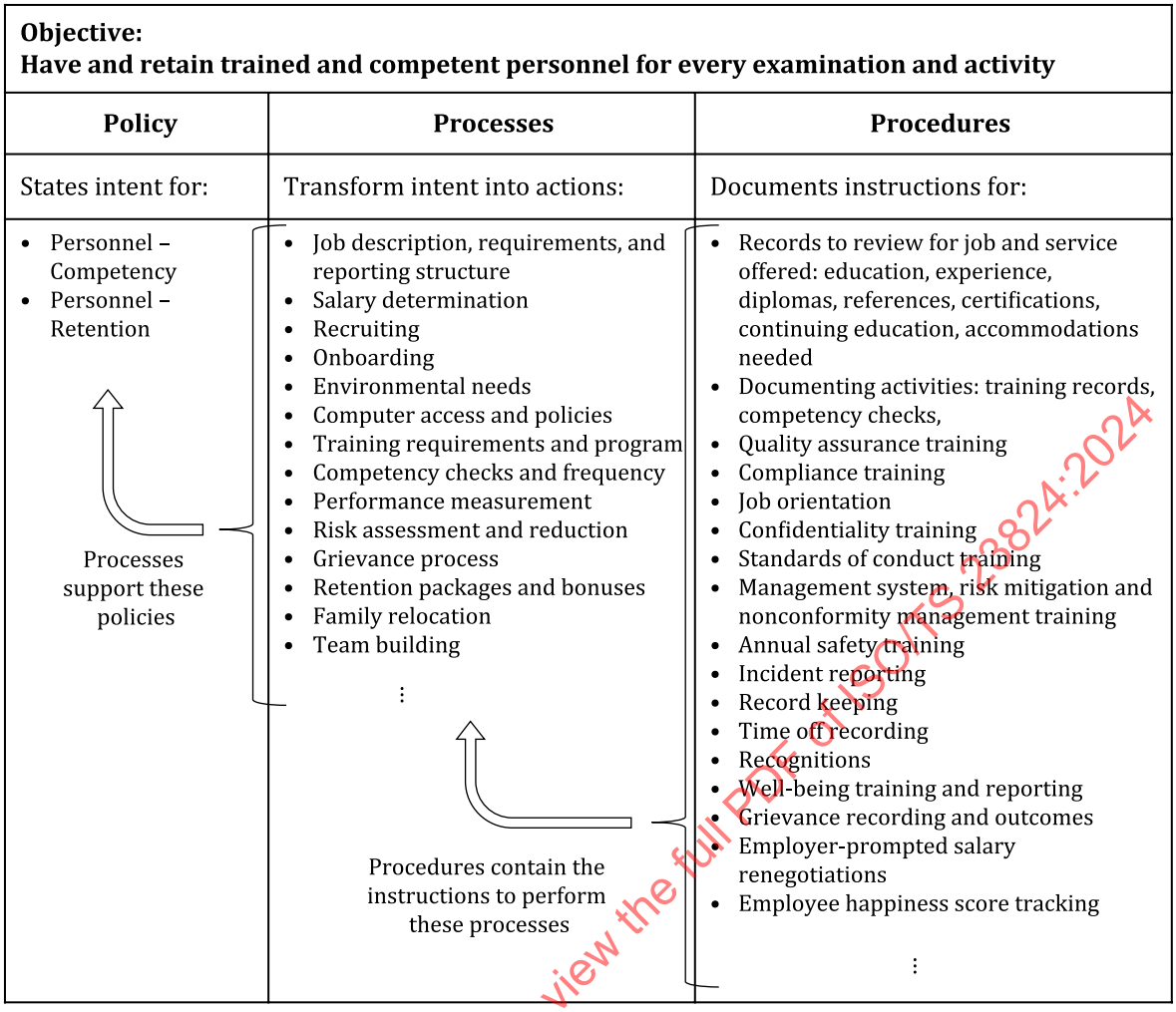

Figure 3 — Examples of policies, processes and procedures for personnel

6.2 Examples of process actions and risks for resource requirements of ISO 15189:2022

Table 3 shows examples of actions that can meet the ISO 15189:2022, Clause 6 requirements as applied to the AP laboratory's processes and also shows examples of risks as they would apply to each respective AP laboratory for those processes.

NOTE 1 The actions and risks listed here are not comprehensive but merely examples for guidance. Conformance with every item in Table 3 does not imply conformance with ISO 15189:2022.

NOTE 2 ISO 22367 provides details for managing risk in medical laboratories.

NOTE 3 ISO 15190 provides details for facility and environmental conditions.

Table 3 — Process actions and risks for ISO 15189:2022, Clause 6

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
6.2 Personnel	— Clarify AP management and other AP personnel's availability. — Ensure current position descriptions for each AP position, including the laboratory director. — Specify any formal arrangement of personnel who perform at locations other than the AP laboratory, e.g. via digital pathology, and manage this arrangement appropriately, including specifying the equipment and IT connectivity involved. — Specify any formal arrangement (e.g. contracts, documentation, logistical protocols) for personnel who also work for one or more other laboratories to prevent risk to the laboratory's activities. — Ensure that external or temporary personnel also work in accordance with management system requirements. — Create a culture of process-based and risk-based thinking in all AP personnel.	— Lack of clarity for AP personnel regarding their duties so that important actions are overlooked or otherwise failed to address. — Not having appropriate records (including documented roles/ responsibilities and training/ competency records) for all personnel, if an examination or diagnostic error occur, or a legal challenge arises.
6.2.2 Competence	— Ensure that all personnel performing examinations or rendering diagnoses are trained, competent and authorized to perform examinations or render diagnoses. — Specify the required competence levels of all AP personnel, including AP personnel who perform examinations on AP and cytopathology samples and AP personnel who render diagnoses based on AP and cytopathology examinations. — Assess and ensure the ongoing competence of all AP personnel, including AP personnel who perform examinations on AP and cytopathology samples and AP personnel who render diagnoses based on AP and cytopathology examinations.	— Incorrect diagnoses rendered from anatomic and cytopathic examinations when there is no means to assess ongoing competence or unrecognized deviations from the documented competence requirements. — Lack of cause analysis for examination and diagnosis nonconformities that are attributed to individual personnel. — Failure to include education and training about the laboratory management system and quality control processes in the onboarding process.

Table 3 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
6.2.2 Competence	— Document the plan of action for any AP personnel, including AP personnel who perform examinations on AP and cytopathology samples and AP personnel who render diagnoses based on AP and cytopathology examinations, when there are significant deviations from the documented competence requirements. — Consider not only technical competence but also competence in meeting management system requirements. — Document the plan for action for any AP personnel when there are significant periods of time where an individual is not practicing (e.g. maternity leave, long-term sickness).	
6.2.4 Continuing education and professional development	— Provide or allow for continuing education and professional development of personnel performing AP examinations and for personnel rendering AP or cytopathology diagnoses. NOTE Continuing education can be obtained in person or virtually, when appropriate.	— Lack of knowledge about or application of new and emerging technologies and methods that would improve processes and services to patients or users. — No opportunities for continuing education for some personnel because others attend too often, or the budget is distributed unequally. — Not allowing for continuing education and professional development in quality management and risk management for all personnel. — Continuing education and professional development programs not monitored for effectiveness.
6.3 Facilities and environmental conditions	— Provide designated areas for storage of samples pre- and post-dissection and processing, gross dissection and tissue processing. — Separate the slide reading areas from the technical processing areas. — Establish control of access to pathologists' and other offices and slide and paraffin archives. — Locate the morgue (mortuary) in an area away from routine AP activities.	— Inadequate separation of AP work areas causing cross-contaminations that can result in erroneous examinations and misdiagnoses. — Distractions arising from inadequate separation of microscope reading areas from technical areas causing mis-readings that can generate misdiagnoses. — Inappropriate access of personnel to the morgue causing problems with how remains are treated.

Table 3 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
6.3 Facilities and environmental conditions	— Ensure access to the area for temporary storage of tissues removed during surgery until transportation to the AP laboratory only by authorized personnel and ensure this area has the appropriate environmental conditions and that these conditions are monitored. — Provide guidance for those managing temporary sample storage areas. NOTE Morgues can be considered temporary storage areas. — Monitor formalin, xylene and other chemical exposure levels in the areas of highest exposure risk (e.g. dissection room, tissue processing area, bulk chemical storage area). — Develop specific instructions for cleaning laboratory areas that might be contaminated with paraffin wax, including the floors near tissue processors, embedding stations and microtomes. — Ensure that AP waste management follows required biohazard controls, including those for radioactive materials. — Follow radiation control measures when X-rays are used in the AP laboratory and when potentially radioactive samples are received. — Evaluate the risk of personnel attending radiology procedures and being exposed to radiation. — Specify the storage and transport requirements for paraffin blocks and glass slides at off-site storage spaces. — Establish the specific storage and transport requirement for all samples, including fresh and fixed tissue, cytology fluid samples, and paraffin embedded tissue (e.g. no shipping without ice to high temperature environments). — Conduct fine needle aspiration clinics for accompanying care partners. — Develop the process for managing visits to the autopsy suite by family, other persons with interest, and law enforcement personnel.	— Proximity of morgue activities (e.g. flow of removal of remains) causing distractions to attention to the technical work. — Inadequacies of temporary storage areas causing: — Sample mishandling — Inadvertent or deliberate adulteration — Storage conditions that affect sample quality — Sample loss — Safety hazards causing either personnel slips or falls, or both, when working in the AP areas or walking through them. — Adverse health effects of aerosol inhalation. — Adverse health effects of AP personnel exposures to toxic chemicals (e.g. staining chemicals, formalin, xylene), radiation and infectious agents.

Table 3 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
6.4 Equipment	— Provide instructions and create records for installation, operational, and performance qualifications of all equipment, instruments, computer systems (including digital pathology). — Create schedules for, and records of, calibrations of measuring instruments as well as for in-house cleaning and externally provided preventive maintenance. — Train all AP personnel on, and authorize their use of, AP equipment and instruments in their respective jobs. — Calibrate ocular micrometres used on microscopes; ensure length measurement using digital cameras or on digital pathology slides are accurate (e.g. for measuring depth of invasion). — Ensure monitors used for digital pathology slide review have suitable display, resolution, brightness and contrast, and that the AP laboratory is aware of, and considers, any differences between monitors used by different personnel. — Although AP testing might not allow metrological traceability to reduce between-method variability, be aware of such variability and mitigate the risk for patients and users arising from such variability. — Remove wax build-up from all equipment, including histology microtomes and microscopes. — Remove mounting compound and tissue shavings from cryostats and frozen section area microscopes.	— Improper equipment maintenance leading to unavailability for AP procedures and services. — Inaccurate measurements of the tissue being examined from uncalibrated or mis calibrated ocular micrometres (or mis calibrated microscope cameras if measurements are done digitally). — Contamination from wax trimmings containing small amounts of tissue or cells. — Failure to consider computer software as part of the equipment.

Table 3 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
6.6 Reagents and consumables	— Follow all specified manufacturer and laboratory requirements for purchased and in-house prepared reagents and chemicals. — Verify the performance of each new formulation or lot of reagents before use or before release of results, as appropriate. NOTE The verification requirement applies to purchased and in-house prepared reagents and chemicals. Verification before release of results can be appropriate for: — xylene in tissue processors, — immunohistochemistry antibodies when control tissues are scarce or difficult to obtain.	— Selection of reagents based on price without considering performance characteristics. — Lack of complete records of reagent management, resulting in inability to thoroughly investigate staining problems or examination errors — Personnel performing examinations over- or under-estimating laboratory-specific antibody specificity or sensitivity. — Antibody clone changes leading to misinterpretations (e.g. new referral laboratory uses less specific TTF1 clone or monoclonal instead of polyclonal Pax8 antibody).
6.7 Service agreements	— Specify and document, in any agreements, the criteria for qualifications of personnel from external sources who will perform examinations or render AP and cytopathology diagnoses and second opinions.	
6.8 Externally provided products and services	— Make formal arrangements for obtaining any referral testing and interpretive AP services not provided but needed for serving patients. — Document the process for sending tissues, blocks, slides, digital images and clinical/patient information to another laboratory for examination or opinion.	— Services chosen based on price and not quality. — Inadequate processes to implement and review services, leading to workload exceeding capacity or expertise and not meeting need of users. — Losing track of sent out specimens. — Delays in obtaining reports.

Table 3 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks in the AP laboratory
6.8 Externally provided products and services	— Ensure traceability of what was sent out and specify instructions for how and when the material(s) is/are to be returned. — Review the record of material sent out to ensure that either reports or samples, or both, are returned in a timely manner. — Specify and document, in any agreements, the services from, and standards for, any external laboratory chosen for referral laboratory examinations and services. — Establish the competence and define selection criteria of referral laboratories providing examinations and, if applicable, AP consultants providing diagnostic opinions (e.g. criteria, reputation, testing methods employed, track record or examinations performed, technical superiority of equipment, scientific excellence, contributor to best practice guideline). — Define the process for actions taken when a requested second opinion significantly disagrees with the AP laboratory's examination result or diagnosis. — Timely notification of the user when second opinion is discordant with original diagnosis. — Record errors made by external providers, mitigate impact on patients, and provide feedback to the external providers.	— Potential for examination and diagnostic errors by referral laboratories that perform examinations and consultants that render AP and cytopathology diagnoses and second opinions. — Inaction about discrepancies between in-house and referral examinations and diagnoses and their impact on patients. — Not notifying laboratory users of changes in referral laboratories leading to false assumptions of reference values or limits of detection. — Not notifying laboratory users of changes in individual consultants, leading to false assumptions of examination thresholds or limits of detection.

7 Process requirements

7.1 Managing processes in anatomic pathology (AP)

AP laboratories need to understand their processes to manage them effectively. Tools that help laboratories to understand and document their processes include process auditing and process mapping. The detail of process maps can range from a) high-level with few activities to b) highly complex, including every activity in a process. Figure 4 shows an example of a high-level process map of an AP operation. Process maps can help users identify process inputs, outputs and interactions, establish quality metrics, and identify potential risks.

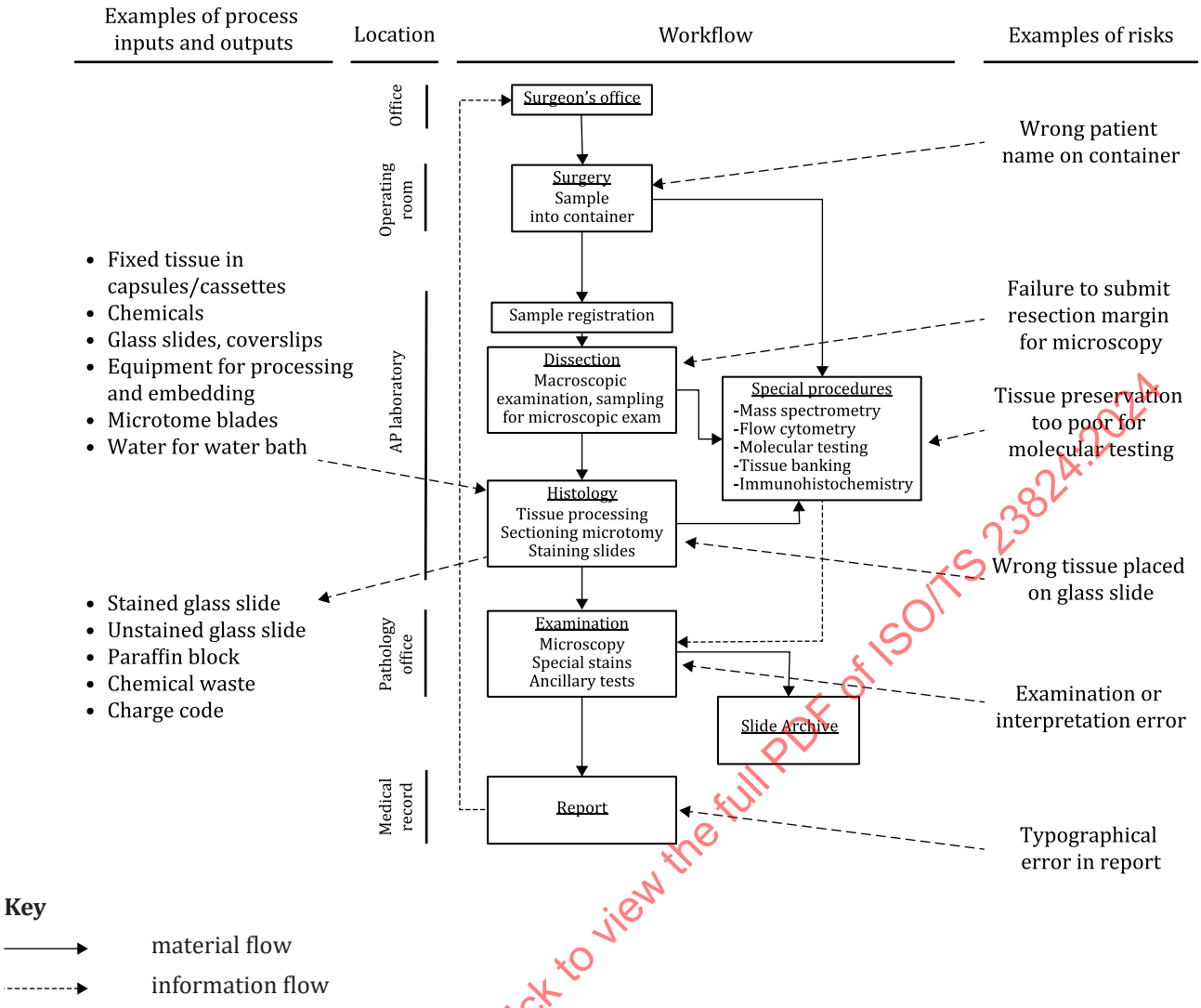

Figure 4 — Process map of an anatomic pathology (AP) operation

A comprehensive list of laboratory processes can assure that all laboratory activities are accounted for in the management system and that all process activities are supported by the necessary procedures. Some processes (often referred to as core processes) directly relate to sample processing and patient care, while others (often referred to as support processes) relate to management of the laboratory (e.g. personnel, supplies, contracts).

7.2 Examples of process actions and risks for the process requirements of ISO 15189:2022

Table 4 shows examples of actions that can meet the ISO 15189:2022, Clause 7 requirements as applied to the AP laboratory's processes and also shows examples of risks as they can apply to each respective AP laboratory for those processes.

NOTE 1 The actions and risks listed here are not comprehensive but merely examples for guidance. Conformance with every item in Table 4 does not imply conformance with ISO 15189.

NOTE 2 ISO 22367 provides details for managing risk in medical laboratories.

NOTE 3 ISO 20658 provides detailed information for sample collection and transport.

NOTE 4 The ISO 20166 series and the ISO 20184 series provide detailed information for samples from particular sources.

NOTE 5 ISO 20387 provides detailed information on biobanking.

NOTE 6 ISO 27799 and ISO/IEC 27002 provide detailed information on information security management in health.

Table 4 — Examples of process actions and risks for ISO 15189:2022, Clause 7

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.2 Pre-examination processes (including requesting examinations and collecting, handling, and transport of samples)	— Define the AP laboratory's pre-examination processes and any pre-examination activities outside the direct control of the laboratory, but which can have an impact on sample quality, examination or diagnosis. — Whenever activities involve samples, consider all the samples an AP laboratory can encounter, which can include: — Fresh (unfixed) and frozen tissues, e.g. sarcoma resections with bone, Optimal Cutting Temperature (OCT) compound-embedded frozen section remnants, brain sample for intraoperative smear; — fixed samples (consider different fixatives, e.g. formalin, glutaraldehyde, alcohol, B5, Zenker); — Paraffin-embedded tissues; — Extracted RNA or DNA; — Cytology smears; — Air-dried or fixed unstained smears; — Fixed and unfixed fluids. e.g. FNAs, synovial fluids. — Develop AP processes in collaboration with perioperative services so that samples removed from patients during surgery are transported to either the specified holding area or the pathology laboratory sample receiving area, or both, in a timely manner in the desired condition. — Establish requirements for warm and cold ischemia time, when appropriate, to assure high quality samples for all applications, especially biomarker testing and genomic medicine. Consider time stamps at different stages of the pre-examination sample route.	— Lack of understanding about which examinations are needed on a small sample; therefore, using up the sample before the desired examinations were performed. — Sample wastage when no process is in place to address rejection of a sample with the submitting user. — Untimely transfer, diversion, or loss of irreplaceable patient tissue before receipt in the laboratory when clear instructions are not provided. — Multiple concurrent samples from a patient inadvertently mislabelled or equivocally labelled. — Misinterpretation of Roman numerals (e.g, Roman numeral two mistaken as Arabic number eleven). — Formalin exposure to personnel who handle surgically removed tissues that are placed into formalin. — Delay to patient results when samples are not delivered to the laboratory in a timely manner.

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.2 Pre-examination processes (including requesting examinations and collecting, handling, and transport of samples)	— Define warm ischemia time locally by multidisciplinary collaboration between pathologists, surgeons, anaesthesiologists, nursing personnel, medical laboratory personnel, and others involved in the process. — Provide laboratory information that states all of the AP laboratory's services, including a detailed listing of examinations provided and the required volume of sample for each examination, as well as the normal cut-off range of each examination's value. — Prepare specific collection instructions for surgery personnel who handle the different types of tissues removed during surgery, to include: — Sample orientation; — Marking margins; — Sending samples fresh if needed (e.g. for frozen section, flow cytometry, certain genomic testing, fluorescence staining, biobanking, research needing live cells); — Using transport containers containing the correct fixative; — Correct sample labelling; — Preparing the examination request (e.g., completion of the request form); — Facilitating sample transport to the laboratory. — Specify the maximum allowable time that surgical samples can be held at the surgery room before transportation to the AP laboratory to minimize sample degradation. — Define critical sample types for immediate transport to the AP laboratory and ensure surgical personnel are aware of their critical nature. — Advise surgeons and other clinical staff collecting samples how to provide samples fit-for-purpose before the procedure, when needed.	

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.2 Pre-examination processes (including requesting examinations and collecting, handling, and transport of samples)	— Provide safety instructions for surgery personnel for handling formalin or radioactive samples. — Define the process for prompt and reliable notification of users when samples are not acceptable (i.e. sample integrity is compromised or other reason to reject sample), retain evidence of such notification and perform or assist with cause analysis to prevent recurrence. — Ensure reliable and consistent sample receipt when laboratory is not staffed around the clock. — Ensure there is an AP sample receiving and accession system (e.g. paper or electronic log) for sample traceability. — Maintain appropriate environmental conditions during transport of sample (including fresh, preserved and fixed specimen, e.g. flow cytometry samples, cytogenetics samples, snap frozen samples). — Ensure sample preservation (DNA, RNA, proteins) for molecular and genomic examinations as well as research applications and biobanking. — Provide information about which specialized tests need a discussion with a pathologist before collecting and sending a sample. — Agree upon and describe the means of communication between AP and surgical personnel (e.g. for frozen section reporting or sample adequacy problems).	
7.3 Examination processes (including validation of examination methods, reference intervals, clinical decision limits)	— Recognize the iterative nature of pathological examination when, after slide or medical history review, repeat gross examination of the surgical specimen is needed. — List the minimum sample requirements for specific types, e.g. minimum amount of tumour (or type of biopsy) required for specific assays (especially genomic testing or flow cytometric immunophenotyping).	— Failure to recognize that both gross and microscopic examination are parts of the examination phase. — Disrupting structural integrity during sample dissection impacting shape, orientation and margins of a surgical sample. — Wrong results when procedures developed in the AP laboratory or modified from a manufacturer's validated method are not validated to work as intended before use on patient samples.

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.3 Examination processes (including validation of examination methods, reference intervals, clinical decision limits)	— Reference the source of minimum sample requirements, e.g. national/ international best practice guidelines. — Prioritize examinations based on clinical information, especially when sample size is small EXAMPLE Liver core biopsies with metastases can require a panel of immunohistochemical stains to determine the origin of the tumour, while liver core biopsies for non-neoplastic disease can require stains to highlight fibrosis, iron, copper or reticulin fibres. — Before use on patient samples, validate that any methods developed by the laboratory or any method that deviates from the manufacturer's instructions work as intended. NOTE 1 Review of digital slides (whole-slide images) can be considered equivalent to review of glass slides when validated for intended use. — Validate image analysis systems and software (e.g. Ki67 proliferation rate, stained cell counts for ER/PR/Her2, architectural pattern recognition and grading, automated uterine cervix cytology screening) and establish criteria for when to re-validate. — Before use on patient samples, verify that any methods, reagents or equipment used according to manufacturers' instructions work as intended. — Establish criteria for periodic review of examinations to ensure they remain clinically appropriate and necessary. — Establish reference intervals, when appropriate, based on latest data and recommendations. NOTE 2 Reference intervals in AP, for example, can be the upper limit of plasma cells in a normal bone marrow or the minimum number of eosinophils in eosinophilic esophagitis. — Ensure timeliness of frozen section service.	— Wrong results when procedures developed by a manufacturer are not verified to work as intended before use on patient samples. — Incomplete or inaccurate diagnosis when laboratory does not ensure its processes remain up-to-date and according to current applicable guidelines. — Differences in diagnostic certainty when AP interpretations are performed by generalist versus subspecialist pathologists or new-in-practice versus experienced pathologists.

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.3 Examination processes (including validation of examination methods, reference intervals, clinical decision limits)	— Document grossing guidelines as part of the examination procedure. — Specify reference intervals for molecular and genomic examinations to enable clinical decision making. — Specify and record clinical decision limits (e.g. cut-offs for PD-L1, ER, Her2 staining).	
7.3.4 Measurement uncertainty	NOTE 1 Measurement uncertainty, as defined in ISO 15189, is a concept that applies to measurands in AP. A measurand is a quantity intended to be measured. Certain examinations in AP are reported as numerical values (or numerical cut-offs are used for interpretation as positive or negative), for example, hormone receptors (e.g. ER and PR), cell surface proteins (e.g. Her2 or PD-L1), Ki67 proliferation indices in neuroendocrine tumours, Breslow thickness in melanomas, mass of parathyroid excisions. NOTE 2 ISO/TS 20914 provides details for estimating measurement uncertainty in medical laboratories. ISO/TR 27877 provides details for evaluating the precision of binary measurement methods and their results. The Joint Committee for Guides in Metrology provides basic and general concepts for metrology.[11] — List the quantitative tests used in AP (e.g. mitosis counts, quantitative or semi-quantitative scoring of immunohistochemical stains, depth of invasion). — Ensure that the reported numerical result (e.g. ER, PD-L1, Ki67) is an acceptable estimate of the value of the measurand. This is of particular importance around clinical decision points. EXAMPLE When a PD-L1 Tumour Proportion Score (TPS) of 49 % prevents a patient from being treated with an immune checkpoint inhibitor used in patients with TPS ≥50 %, uncertainty of that examination result can lead to treatment being erroneously withheld.	— Ignoring or failing to assess the relevance of measurement uncertainty of measured quantity values in AP examinations. NOTE Uncertainties in the system, whether measurable or not, can affect examination results and impact diagnoses and patient care when they are not identified and action is taken to minimize them. For example, the Guideline for Estrogen and Progesterone Receptor Testing in Breast Cancer [12] acknowledges variability in treatment success for low ER-positive tumours and uncertainty about the "true" negative status of negative results, and proposes additional strategies to promote optimal performance, interpretation, and reporting of cases with low or no ER staining results including establishing a laboratory-specific standard operating procedure describing additional steps used by the laboratory to confirm or adjudicate results.[12]

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.3.7.2 Internal quality control (IQC)	— Define and document the quality control plan and procedures for each examination procedure used. — Define and document the case peer review frequency and process to detect discrepancies or interpretive errors and define the acceptance criteria and risk categories. — Consider risk-based IQC for reviewing cases, since reviewing only a certain percentage of random or pathologist-selected cases often results in only malignant or clear-cut cases being reviewed. EXAMPLE Examinations resulting in a subsequent diagnosis of malignancy are rarely overturned by IQC. Therefore, routine second review of all first-time malignant diagnoses can have low yield. Risk-based IQC can instead aim to discover examinations resulting in false-negative (benign) diagnoses of malignant diseases. They can pose a higher risk because a patient might not seek further care despite having a condition that requires treatment. NOTE Consultations can be a component of IQC for stains, slide preparation and equipment.	— Lack of internal quality control for all activities in the process that contribute to examination results or diagnoses, leading to incomplete or incorrect examination results or diagnoses being released, which, in turn, impacts patient care and outcomes. — Consensus conferences that reflect the examination result or diagnosis of the most senior, most respected or most outspoken pathologist, and which might not be the correct examination result or best diagnosis. — Internal quality control being perceived as punitive or shameful, creating an incentive to hide or downplay examination, diagnostic and other errors.
7.3.7.3 External quality assessment (EQA)	— Participate in formal EQA schemes, interlaboratory comparisons or suitable alternatives for all examination methods used. NOTE Where no formal EQA schemes exist, alternative options can include clinical comparison at multidisciplinary conferences, comparison of cytology diagnoses with subsequent histology diagnoses, subscription to an online digital pathology consensus diagnosis or case discussion program, or comparison of diagnosis indicated by an IHC stain with the diagnosis indicated by other stains in the panel which are covered by a formal EQA scheme.	— EQA not covering the entire end-to-end examination process, implying that the AP service is more competent than it actually is. EXAMPLE Good performance in a technical staining EQA scheme does not indicate that personnel interpreting the stain are competent to do so.

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.4 Post-examination processes (including result reporting and amendments to results)	— Use standardized reporting templates and measurements whenever possible and available (including cancer protocol templates for standardized reporting) and indicate version of the classification system used (e.g. edition, year). — Incorporate methodology and result interpretation data into reports of ancillary and molecular tests. — Include tumour percentage in the material used for molecular testing. — Define what constitutes a critical result and how it is to be communicated. — Define storage requirements specific for AP for all sample types, including residual sample storage conditions when the AP laboratory incorporates biobanking. — Specify which measurement procedure was used when different measurement procedures can give different results (e.g. Ki67 proliferation index counted manually versus determined by digital image analysis). — Define a process that ensures timely inclusion of any referral or second opinion reports and any additional test results into an updated report. — In laboratory reports, distinguish between results or clinical advice that the AP laboratory provides to its users and results or clinical advice that consultants provide to the AP laboratory. — Document a process for amending released reports when an error is found, including who has authority to authorize amended reports, how the amendments will be identified in the report, and how the user will be notified on the amendment. — Include a comment in reports as to whether the paraffin block is likely to contain enough tissue for molecular testing. — Define the process for removing samples from storage to use for research and for returning them.	— Delay in practitioner action and patient notification when discordant results can cause either a change in diagnosis or treatment, or both. — Users are not aware of amended report, leading to wrong treatment. — Lack of traceability of amended reports creating potential liability for treating physician because the examination result or diagnosis on which treatment decision was based is expunged from the record and replaced by the amended report. — Not identifying in the report that an examination result or diagnosis was provided by a consultant. — Misfiling AP samples or not storing them for the legally required retention period, meaning subsequently requested examinations or participation in research might not be able to be performed. — Traceability of identification not maintained from primary sample to extracted DNA. — Biohazard exposure from unfixed, air-dried cytology smears. — Cutting through a paraffin block, so that there is no tissue available for subsequent testing, including genomic testing, which can result in incomplete examinations, diagnoses, delayed patient treatment or patient harm through need for re-biopsy.

Table 4 *(continued)*

ISO 15189:2022 subclause	Actions for process management to meet ISO 15189:2022 requirements in the AP laboratory	Examples of risks management in the AP laboratory
7.5 Nonconforming work	NOTE Nonconformities can be related to any requirement (e.g. requirements for training, competence, environment, safety, equipment, examination processes, results, records or management system). When the AP laboratory includes providing a diagnosis as part of its scope, nonconformities can also be related to the diagnosis provided. — Identify the person responsible for deciding when results are at risk. — Assess the risk of nonconforming work and establish criteria for determining the need for corrective action. — Specify timeframes in which nonconformities should be investigated and rectified and how long a result should be withheld.	— Corrective action only addressing nonconforming work with high severity of harm while neglecting nonconforming work with low severity of harm but high frequency of recurrence.
7.6.3 Information systems management	— Ensure all information management systems are managed in accordance with ISO 15189:2022, including digital pathology systems, electronic quality management systems, and inventory management systems. — Specify the storage and data security requirements for digital images. — Ensure functional, validated and secure bioinformatics pipelines for genomic data and emerging machine learning technologies, where applicable. — Use offline reporting templates to enter, print, and release reports manually during extended system downtimes.	— Potential software issues impacting digital process interpretation. — Failure to deliver the right information to the right person at the right time.
7.7 Complaints	— Enter all formally submitted and orally expressed complaints into the laboratory's complaint process. NOTE Complaints about AP are sometimes orally communicated to AP personnel at clinical conferences or in physician lounges.	— Complicated complaint reporting procedures can prevent reporting of high frequency, low severity events that adversely affect laboratory services and users.