IT'S TIME TO DO BETTER

A PRACTICAL GUIDE TO OPTIMIZING THE PRE-ANALYTICAL WORKFLOW

MILESTONE
HELPING PATIENTS

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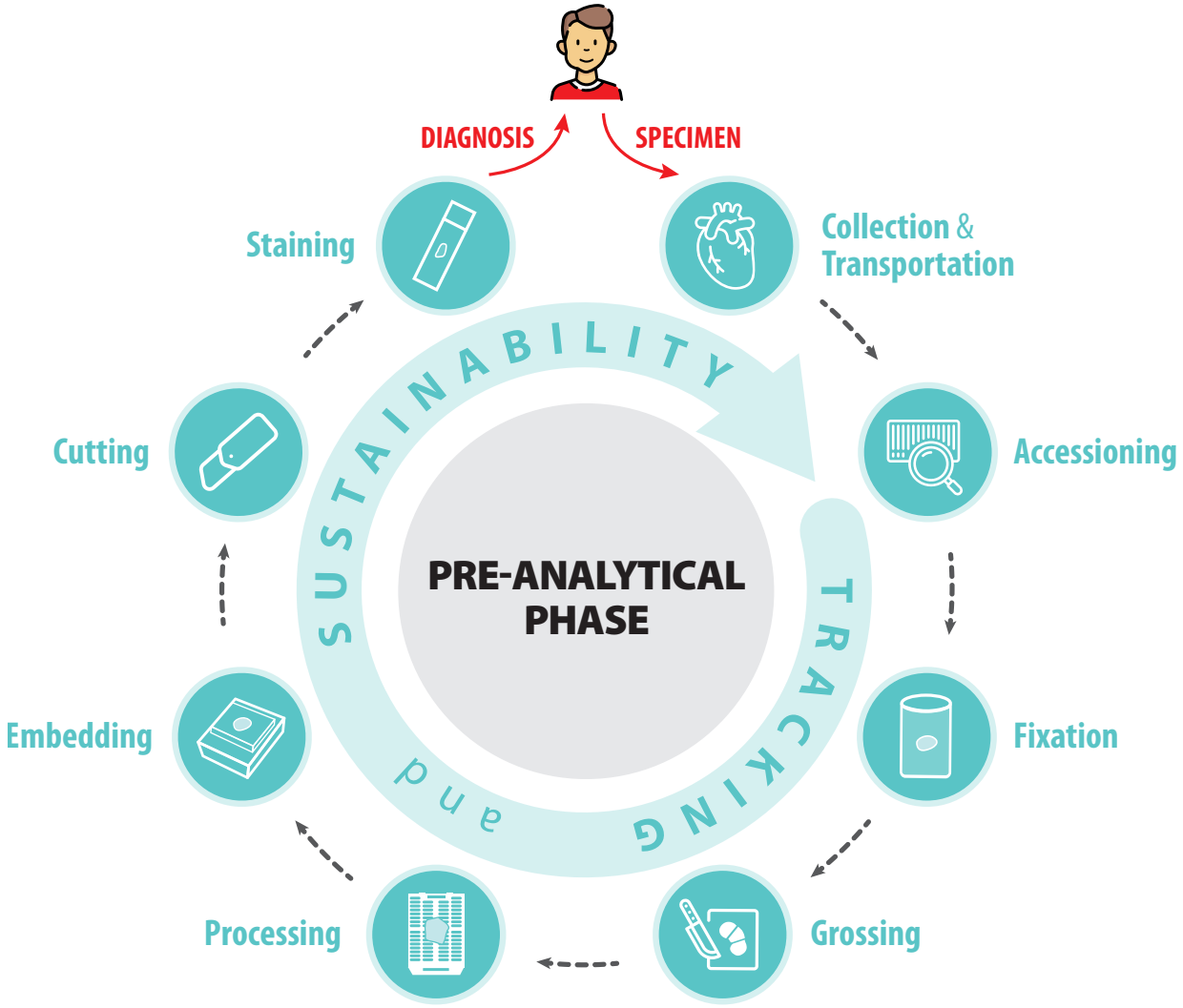
Introduction

Pre-analytical phase, the most impactful, yet often forgotten phase

Anatomical Pathology (AP) is a scientific discipline that studies and identifies changes in organs and tissues caused by intrinsic and extrinsic factors that lead to cellular physiological disorders. Giovanni Battista Morgagni (1682-1771) is known as the father of modern anatomical pathology for his work linking post-mortem findings to the causes of disease.
Pathologists, the physicians who study the body's tissues, invented over the years a variety of "staining techniques" to identify under the microscope the different cell and tissue structures. [1,2] Such techniques, although powerful, have seen minor evolution for many decades resulting in a lagging technological development that has relegated AP to a secondary role. However, in the last 3 decades, AP has been transforming itself with the advent of immunohistochemistry first, and more recently, the incorporation of genetic and molecular analyses into the diagnostic mainstream. Such significantly increased diagnostic capabilities have established AP as a crucial and necessary discipline within medical and clinical boards. Compared to few years ago, diagnostic and prognostic testing have therefore steadily increased in usage. [3] The goal is to precisely identify tumours and their specific targets, thereby designing personalized therapy, known as "precision medicine". Technological advances continue to raise the bar for high-end analyses, such as AI interpretation reporting, epigenetic screening, clinical oncology NGS and CRISPR. However, it is often forgotten that the reliability of these high-level tests depends unequivocally on how the biological material is handled from its collection in the operating room through the stained slide. Milestone, with its deep-rooted expertise and unwavering presence in the pre-analytical, has wholeheartedly embraced and champions this mission. This is why Milestone is convinced that the era of *IT'S TIME TO DO BETTER* must begin now. [4] This vision becomes a reality through the delivery of cutting-edge solutions that revolutionize workflows, empowering pathologists, histologists and technicians not only to meet their goals but to exceed them, setting new benchmarks of excellence:

» BETTER **SPECIMEN QUALITY**
» BETTER **WORKFLOW EFFICIENCY**
» BETTER **OPERATOR AND SPECIMEN SAFETY**
» BETTER **SPECIMEN TRACKING**

Tissue specimens obtained during surgical procedures are a crucial source of molecular information about the patient and their disease. After surgery and before the tissue arrives at the AP labs, factors such as collection time, ischemia time, transport duration, fixation time, fixative ratio, and temperature can impact tissue quality. Often, these factors are not recorded nor mentioned, despite being crucial parameters that influence the diagnosis. They are as important as the grossing procedure, tissue processing, embedding, microtome sectioning, and staining.
Suboptimal handling of the specimens can impair the quality of the material, introduce cross-contamination and artifacts, and compromise the integrity of specimen DNA/RNA, thus affecting molecular analysis data. Consequently, patient safety may be jeopardized and the quality of diagnoses impaired. [5] For these reasons, modern technologies must provide medical teams with scientific tools that cover all the steps of the pre-analytical phase, from the moment a patient's specimen is taken, through the preparation of slides. Milestone is committed to do better across the specimen journey from operating room to the slide, throughout scientific tools that standardize, track, and optimize every step of the journey.



Despite some preliminary efforts to modernize the pre-analytical phase, still much is to be done. Errors still occur in both cytopathology and surgical pathology, significantly contributing to diagnostic inaccuracies and remaining a major concern for reliable diagnoses. A comprehensive review on cancer cytopathology found that 87% of errors were related to pre-analytical processes. [6]

Paradoxically, the pre-analytical phase receives less attention in educational and quality improvement programs and has fewer scientific publications. In addition, unlike clinical labs that can request additional urine or blood specimens, surgical pathology faces unique challenges. Once tissue is removed, if details are not recorded and appropriate sections are not taken, they are lost forever, as highlighted in Rosai and Ackerman's Surgical Pathology book. [7] Until now, laboratories have had no way of knowing what happened to a specimen if it wasn't recorded. When something is discovered to be wrong, it may be too late, and the material may be compromised for good. [8] A typical experience in every lab is realizing that a cassette is missing at the end of the day, causing techs to frantically search for it. This underscores the importance of integrating equipment into the lab's workflow to ensure specimen tracking from start (specimen collection) to finish (final diagnosis), prompting medical societies to advocate for change.[9] [10] Introducing "checkpoints", such as automatic cassette counts and barcode detection, would ensure comprehensive collection and documentation of case numbers. High-quality image documentation during grossing would make every detail consistently accessible and easily retrievable for consultation.

Other sources report that controlling and reporting alterations of pre-analytical variables have been done occasionally or only for certain tissues, such as breast cancer specimens. However, if it is important for one type of molecular test for one type of cancer, it is likely important for all molecular tests across all cancer types.[11] [12] These measures must be applied to all tissue types. In fact, the control of pre-analytical steps is growing in importance, supported by the CAP (College of American Pathologists), which established the PPMPT (Preanalytics for Precision Medicine Project Team) to develop a basic set of pre-analytical recommendations.[13,16]

Many labs have independently attempted to develop strategies and individual solutions to address these tasks. However, to ensure consistency, the role of industry partners becomes crucial, offering an unprecedented level of support for the pre-analytical phase. In this context, few companies have demonstrated the clear mission of helping patients and professionals, developing scientific tools to address these complex tasks.

Every laboratory should have access to solutions that enable operators worldwide to control and record the described 'checkpoints' related to the pre-analytical phase. This would provide the medical team with a comprehensive dataset that outlines the entire life cycle of a specimen, allowing staff to make better-informed decisions and achieve superior outcomes in favour of more accurate diagnosis. Once this is ensured, modern pathology will deliver reliable diagnoses thorough analytical and post-analytical evaluation. [13]

This technological advancement will enhance laboratory efficiency by providing data that enables better workload planning to address rising personnel shortages and the increasing number of cases. [14] This aligns with the common need to reduce unnecessary tasks that significantly impact laboratory performance and operational costs. In addition, these objectives should align with the growing demand for laboratory sustainability. For example, integrating fewer toxic reagents into laboratory practices not only promotes environmentally friendly processes but also significantly enhances operator safety, contributing to a healthier overall work environment.

Each step of the pre-analytical phase can be crucial for the diagnostic outcome. But far too much is still based on "eye-balling" and on procedures that have not been adjusted over time. It's time for a change, because we cannot afford not to. Not only pathologists, but also technicians, nurses, and the entire team involved in the diagnostic workflow should be an active part in improving the pre-analytical process.

The purpose of this eBook is to analyse the various steps of the pre-analytical phase, explore the current challenges faced in pathology laboratories, and propose actionable solutions to ensure optimal diagnostic quality.

The pre-analytical phase has now gained its rightful importance as an integral part of the medical processes, particularly concerning the 'Chain of Custody' of specimens. This is because "precision medicine" demands equally "precise diagnosis".

01.

Specimen Collection and Transportation

The journey of a specimen toward a pathological diagnosis begins with the very first step of the pre-analytical process: collecting the specimen from the patient in the Operating Room (OR) and transporting it to the Anatomical Pathology (AP) lab.This phase is crucial because it greatly influences the results. It is estimated that 60-70% of all problems in diagnostic laboratories are attributed to the pre-analytical phase, with many occurring during the initial steps. [15] Several factors may lead to suboptimal tissue quality, such as Warm Ischemia Time - the period when tissue remains at body temperature with reduced blood supply- and Cold Ischemia Time - the period from tissue removal from the body until preservation. Both must be considered, as they determine stress and changes at the molecular level of the tissue. [16]

Once the specimen is removed from the patient *(Figure 1)*, it must be put in a fixative (usually buffered formalin) before being transported to AP. Currently, this process is performed manually, holding the nurse responsible for filling the container with formalin.

This task is highly dangerous for the nurses, as it exposes them to toxic formalin fumes. In fact, formalin is declared carcinogenic, mutagenic and reprotoxic to humans by several agencies, including IARC (International Agency for Research on Cancer), NCI (National Cancer Institute) and the EU (European Union). Since April 2015, it has been classified as a category 1B carcinogen and a category 2 mutagen under EU regulations. [17]

In addition, like all manual processes, this activity is operator-dependent and thus poorly standardized. The lack of standardization increases the risk of using incorrect amounts of formalin in relation to the specimens' size. This significantly affects the diagnostic process, as using formalin without a defined ratio leads to unstandardized fixation and an unreliable process with waste in both reagents and money. [18]

Figure 1. Biopsies and larger specimens are collected from the patient during surgical procedures.

Another risk of manual handling is the spillage of formalin inside the operating room posing a high probability of contamination that may necessitate temporarily closing the OR for cleaning and disinfection protocols. This could result in significant delays and loss of time for the multiple departments involved, thereby seriously impacting operational efficiency.

Due to stringent regulations requiring operators to minimize their exposure to formalin or switch to less hazardous alternatives, combined with the numerous drawbacks of manual procedures, there is a growing imperative to adopt new approaches. However, little progress has been made in improving this critical step. At Milestone we believe it's time to do better using dedicated tools to tackle the specimen handling. These units dispense formalin within properly ventilated compartments, significantly reducing the exposure to the fixative agent and minimizing complications from accidental spillages *(Figure 2)*.

Automating the filling process leads to standardized procedures and precise formalin dosage based on specimen weight, eliminating reagent wastage. Moreover, this automation saves time by enabling operators to focus on added value tasks, enhancing daily workflow efficiency.

Figure 2. Example of an automatic formalin dispensing system inside a protected area.

An additional vital aspect is the possibility to document specimen collection by associating all details and information of the process with the patient's ID. Several parameters are essential for effective traceability, including operator's name, date, time to fixation, temperature, and quantity of fixative used per specimen. Through a direct link, these data points are automatically transferred to the lab's LIS, facilitating an easy and fast reconstruction of the specimen's journey. This also prevents frequent critical mismatch errors and ensures full chain of custody.

Another important aspect is related to the recent interest in molecular biology and bio-banking, which has been steadily increasing. [19] However, for these studies to be effective, it is important that biological specimens are preserved in a fresh state, without the use of formalin, which can compromise the integrity of the tissues.

To meet this need, new systems employing advanced vacuum technology have been developed. These innovative tools are designed to maintain the optimal condition of the specimens, ensuring that they remain perfectly preserved at controlled temperature (4°C) for up to 48/72 hours. [20] In these systems, the absence of formalin guarantees the safety of the operator. Moreover, eliminating the need for the fixative reduces costs, positively impacting the laboratory's sustainability.

After the initial phase of specimen collection from the Operating Room, the next phase involves transporting the specimen to the pathology laboratory *(Figure 3)*. The safety of the specimens is paramount to maintaining their integrity. This is guaranteed using secure containers, essential for properly preserving the tissues and, if necessary, starting the fixation process. Additionally, during transport, it is crucial to ensure that any personnel handling the specimens do not come into contact with the biological material or formalin.

Milestone offers specimen transportation in either rigid buckets or bags.

The rigid buckets are spacious containers available in various sizes and equipped with specialized openings, such as custom-designed valves that facilitate the easy dispensing of formalin while protecting the operator from potential exposure to toxic fumes during both filling and transportation. However, these solutions can be problematic because containers are often too bulky and occupy a lot of space.

For this reason, vacuum collection of specimens in plastic bags is a valid alternative to buckets. [21, 22]When sealed, these bags assure optimal preservation of the specimen, prevent tissue drying and fixative leakage, and minimize storage space. [23] Additionally, many of these bags are also reusable for the final storage of remaining specimens.

To enhance safety during small biopsy collection in both hospital ORs and ambulatory surgery centres, small containers pre-filled with formalin are also

Figure 3. Specimens must be transported under controlled and safe conditions.

available from Milestone. These containers include a second layer above the formalin that does not mix with it and effectively reduces toxic fumes, ensuring the operator's safety when opening the containers and placing biopsy specimens inside.

Meticulous monitoring and control of the transport are essential to manage variables effectively, protect the specimen from damage, and ensure comprehensive traceability. It is therefore crucial that the specimens are transported with temperature control, ensuring that the range indicated by the official guidelines of 4° Celsius (39.2° F) is respected, as well as the transportation timelines.[19] [24]

To achieve this, monitoring systems have been implemented to track the specimens throughout their journey.

These systems travel with the specimen and, upon arrival at the destination laboratory, provide the technician with the comprehensive information needed to assess the transportation conditions *(Figure 4)*. This ensures that the laboratory technician can be confident the specimen's quality has not been compromised, with all relevant information accurately documented and securely stored within the specimen's chain of custody.

Figure 4. The importance of tracking the transport of specimens from the OR to the AP lab.

IT'S TIME TO DO BETTER

Do better now in **specimen handling!**

Milestone sets the standard for specimen handling excellence, offering exposure-free operations, formalin-free solutions and full documentation of specimen weight, time to fixation, formalin ratio and start of specimen tracking.

DISCOVER **MILESTONE SOLUTIONS**

UltraSAFE *Automated Formalin Dispensing System*

UltraSAFE is an automatic and enclosed system that dispenses fixative in dedicated buckets. The automatic, standardized and documented processes allow OR personnel to handle specimens in complete safety, with no exposure to formalin fumes.

Brochure
Video
Webinar

SealSAFE *Fixative Filling and Vacuum Sealing System*

SealSAFE is an automatic system which seals specimens under vacuum, in dedicated bags, with or without fixative dispensing. The enclosed and vented chamber protects operators from formalin exposure.

Brochure
Video
Webinar

DISCOVER **MILESTONE SOLUTIONS**

TissueSAFE plus *Vacuum Sealing System*

TissueSAFE plus is an automatic vacuum sealing system that allows users to preserve fresh tissues in their natural state, without fixatives, in dedicated bags.

Brochure
Video
Webinar

FormSAFE *Safe Prefilled Formalin Containers for Biopsies*

FormSAFE is an innovative prefilled container with formalin designed to collect and transport biopsies. It includes a second stratified fluid component that floats above the formalin, preventing fixative fumes from escaping the container.

Brochure

Data Logger Card *Time/Temperature Data Logger*

The Data Logger Card can be activated at the start of the shift and then placed into the specimen's transfer box. It continuously monitors and documents tissue temperature and transfer time from the OR to the AP lab.

02.

Accessioning

Accessioning is the receival of patients' specimens delivered to the AP lab. They are sorted, barcoded and entered into the Laboratory Information System (LIS). During accessioning, specimens undergo a "check-in" process where they are officially recorded and tracked. Ideally, this registration system should be used to track specimens throughout the various pre-analytical and analytical stages of laboratory processing, including grossing, tissue processing, embedding, staining, molecular analysis, and the entire diagnostic workflow. However, as of now, this level of traceability is not yet implemented. Biological materials, whether solid or liquid, include specimens received from the same hospital or clinic where the AP lab is located, as well as from external institutions and specimens for research studies *(Figure 5)*.

Figure 5. A large volume of specimens is ready for the accessioning step.

Accessioning is a crucial pre-analytical step because it ensures specimen safety through accurate and efficient identification, from initial receipt to final diagnosis. Any identification errors made at this stage will persist throughout the entire process, potentially jeopardizing the accuracy of the diagnosis. [25]

Besides the "specimen check-in," specimens sent for accessioning must meet specific quality criteria. There is an initial selection process that may result in the rejection of sub-optimal material, which could produce inconsistent results and lead to incorrect diagnoses. Examples of these specific quality criteria include:

- Specimen improperly labelled or mismatched with the requisition form (probed to be the first source of error).
- Improper collection or fixation.
- Incorrect volume of fixative.
- Incomplete test requisition.
- Improper transportation.

Technicians responsible for this step must exercise special care, ensuring accuracy to eliminate errors. They need to verify that the correct material and patient information are received and confirm that the appropriate tests are ordered.

Accessioning is typically performed at the entrance of the AP lab, in a dedicated room or area *(Figure 6)*. Here, the specimens are assigned a unique"case identification number" – the case ID. This number uniquely identifies the specimen and is used for all procedures, analyses, and handling of the specimen until the case is signed-out. The unique case ID facilitates specimen tracking throughout the entire diagnostic process and allows for the retrieval of images, comments, annotations, and the case diagnosis from the LIS at any time for future clinical reference. This remains theoretical, as only a limited number of laboratories currently have

the necessary technology in place to support such comprehensive traceability.

Moreover, the case ID helps keep the patient's name confidential, safeguarding privacy and preventing potential issues related to homonymy. [26]

This procedure is mandatory for enrolling every specimen in the AP Laboratory Information System, enabling technicians and pathologists to proceed with specimen grossing, processing, staining protocols, molecular analysis, and the entire diagnostic process as planned.

Figure 6. Example of accessioning area.

Despite its importance, the accessioning step has not always been given the value it deserves. In the past, the accessioning stage was done manually case by case, requiring staff to match documents with patient specimens or vials and order label printing through LIS software. In many instances, the label printing was the only documented and "automated" step, while the rest of the process was manual and repetitive, increasing the risk of errors, particularly in high-volume laboratories. Additionally, there was typically no photo documentation or formal proof of receipt for the specimens.

A variety of systems and software solutions have been specifically developed and adapted for use in AP. First, handwritten labels are being replaced by printers that generate either alphanumeric code or 1D/2D barcodes for labelling the received specimens. At a later stage in the process, these codes will be printed with dedicated printers on both cassettes and slides, ensuring a complete chain of case identification and documentation for the specimen. Accessioning labels, cassettes, and slides printers' software must seamlessly interface with the LIS to ensure effective communication throughout the workflow. [27]

Although several improvements have been made, a lot still relies on manual operation. It is time to do better in accessioning by using modern tools to accurately track and trace the specimen at the arrival to the AP lab. Milestone has developed systems capable of automatically capturing specimen's container information. The accessioning staff only needs to place the specimen's container in a designated position, after which the system automatically reads and records all the information on the container, such as labels, codes or notes. *(Figure 7)* This approach prevents the loss of important information and ensures that everything is properly tracked, as the data is saved within the specimen's clinical history in the LIS. New devices enable automatic calculation of fixation times, providing valuable insights to ensure specimens meet the eligibility criteria.

Figure 7. Example of automatic accessioning tracking system.

Additionally, it helps prevent specimen/code mismatches, incorrect labelling, and patient misidentification errors, streamlining the process and enhancing workflow efficiency.

Therefore, not only incorrect transfer and collection but also improper accessioning and identification can lead to invalid analytical results, inappropriate diagnoses, consequently adversely affecting patient care.

IT'S TIME TO DO BETTER

Do better now in **specimen accessioning**!

Milestone introduces an advanced automatic tracking tool to streamline and accelerate specimen accessioning. This innovative system efficiently collects comprehensive information from specimen containers, ensuring complete and accurate documentation.

DISCOVER **MILESTONE SOLUTIONS**

V-Tracker *Automatic Vial Scanner*

V-Tracker is an automatic tracking system that collects details and information from the specimen's container through a 360° image.

Brochure

Video

03.

Fixation

Fixation is the initial chemical process applied to a histology specimen. Its purpose is to preserve tissue morphology and cell structure.[28] Fixation halts autolysis and tissue decay, coagulates soluble and structural proteins, and binds molecules to better prepare the tissue for subsequent processes such as dehydration, fat clearing, and wax infiltration. This process is crucial for stabilizing the tissue, ensuring its preservation for years. Moreover, fixation enhances the tissue's ability to undergo staining processes effectively.[29]

The fixative of choice in pathology is formaldehyde, known as formalin when dissolved in water at a specific concentration, although it has some drawbacks. Formalin reacts slowly and penetrates tissues at a limited speed, particularly in the presence of fatty tissues. This can result in improper and incomplete fixation, particularly when tissues are inadequately exposed to formalin tissue or insufficiently soaked in the fixative solution.[30]

Figure 8: Formaldehyde has been classified as a category 1B carcinogen and a category 2 mutagen under the EU Regulation, effective April 2015.

Formalin causes extensive molecular modifications, particularly through crosslinking, which can affect protein antigenicity. This necessitates post-treatment processes like antigen retrieval and careful adjustment of antibody dilution to ensure robust staining intensity. Finally, as mentioned in the previous chapter, formalin is recognized as a carcinogenic substance. *(Figure 8)*

The outcome of fixation has a significant impact on the analytical phase: staining and molecular analysis are directly related to the quality of tissue fixation. Therefore, over-fixed or poorly fixed tissues can both influence the pathologist's interpretation of results, potentially leading to unreliable diagnoses and incorrect drug treatments. *(Figure 9)*

If formalin is added to tissue during collection, the fixation process may already start. However, the fixation must continue for a period longer than collection and transport duration, depending on the tissue type, size, and dimensions.[31]

In routine practice, immediately after tissue collection in the operating room, tissues are placed into a container filled with fixative. This is known as the pre-fixation step. Typically performed manually without monitoring specific parameters, this step is prone to pre-analytical errors. It primarily serves to preserve the tissue during its transfer to the AP lab, where the formal fixation process is then carried out.[32] Once the tissue arrives to the AP lab, being still uncut, the fixative reaction may have occurred only within the initial few millimetres of the tissue.[33] The real fixation process begins only after the surgical specimen has been cut open, dissected, and placed in plastic cassettes. These cassettes are then loaded into a tissue processor, where the fixation process is completed, either at room temperature or with heating.

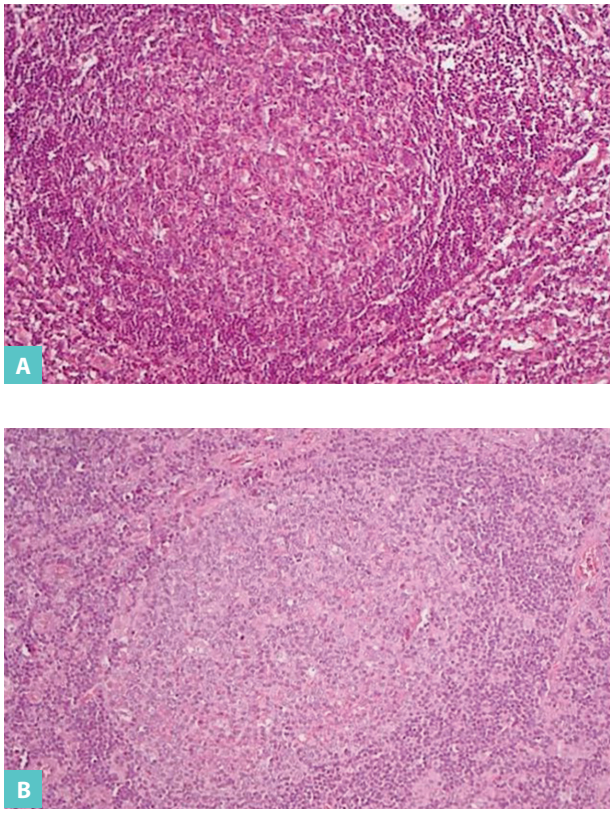


Figure 9: Example of how fixation significantly affects the morphology of the cells. A lymph node with a germinal centre stained with HE, treated with an improper fixation procedure (A): cells lack contrast, exhibit altered cellular morphology and display numerous artifacts. The same lymph node treated with an optimal fixation procedure (B), showing good cellular morphology and satisfactory HE staining. (Institute of Pathology and Molecular Pathology, Helios Universitätsklinikum Wuppertal, Germany).

Numerous variables affect the fixation process and can significantly impact the results. Both pre-fixation and fixation parameters must be carefully controlled to ensure optimal and consistent conditions for tissue preservation. A meta-analysis found that 15 pre-analytical variables can impact immunohistochemistry assays, such as fixation time, temperature, pH, type of fixative and fixation delay. It is therefore evident that controlling these parameters allows for precise, reliable and consistent tissue preparation toward the final diagnosis.

For example, it's crucial to know when the tissue collection began in the operating room, and to assess any potential fixation delays. Such delays can lead to tissue alterations which can significantly compromise the quality of the tissue.[34]

The tissue-to-formalin ratio is another important parameter. Recent studies have shown that fixation is more dependent on time and temperature than on the volume of fixative used. Fixing tissues with a 1:2 ratio of tissue volume to NBF (neutral buffered formalin) volume for 48 hours at 20-22°C (52-54 °F) is sufficient to achieve effective fixation and subsequent infiltration.[35] Therefore, optimizing and standardizing the formalin ratio is essential to achieve robust results, minimize reagent waste, and reduce laboratory costs.

Microwave fixation has proven to be highly effective, completing the fixation process efficiently and safely.[36, 37] Similarly, experiments using controlled temperature conditions - both cold and warm fixation - have shown preliminary evidence of superior preservation of nucleic acids and improved maintenance of other macromolecules, such as phosphoproteins.[38]

It's time to do better fixation. Milestone has transformed this concept into automated systems designed to optimize fixation with reproducible, effective, and standardized protocols. This advancement enhances tissue processing workflows, allowing fixation to be included or excluded based on reliable fixation time data.

IT'S TIME TO DO BETTER

Do better now in **specimen fixation**!

Milestone is committed to delivering solutions that standardize and control the specimen fixation process, ensuring complete traceability of parameters while optimizing formalin levels for enhanced consistency.

DISCOVER **MILESTONE SOLUTIONS**

MAGNUS *High Throughput Tissue Processor*

MAGNUS is a fully automatic tissue processor with two retorts and two robotic arms for continuous batch loading. The dedicated wax retort eliminates the need for time-consuming cleaning cycles, improving laboratory productivity and drastically reducing operational costs while achieving unmatched uptime.

Brochure
Video
Webinar

LOGOS EVO *Advanced Tissue Processor*

LOGOS EVO is an advanced dual retort tissue processor for dual run mode. Rapid processing and high safety standards for both the operator and tissues ensure optimal results while achieving significant cost and time savings.

Brochure
Video
Webinar

DISCOVER **MILESTONE SOLUTIONS**

LOGOS One EVO *Smart Tissue Processor*

LOGOS One EVO is a dual-retort processor equipped with conventional heating technology. It ensures a more efficient workflow and optimizes operator time, particularly in the dual run mode.

Brochure
Webinar

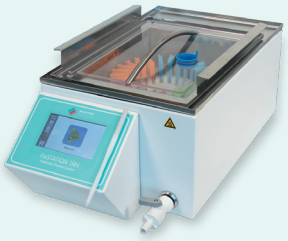
KOS *Multifunctional Tissue Processor*

KOS is a multifunctional microwave tissue processor: rapid tissue processing and decalcifications are the two most popular applications.

Brochure
Video
Webinar

FixSTATION 1RH *Automatic Tissue Fixation System*

FixSTATION 1RH is an automatic bench top system engineered to optimize and standardize the fixation step. The tool ensures accurate and comprehensive documentation, which is readily available for specimen traceability.



Brochure

04. Grossing

After the specimen is received and accessioned in the laboratory, it undergoes the grossing phase.

Grossing involves several important tasks, including the reduction of the surgical specimen, precise cutting, selection of the specimen area and macro documentation *(Figure 10)*. [39]

Due to its importance worldwide, this step is typically performed by pathologists or pathologist assistants. In some countries, trained technologists may also gross specimens, but only after completing a specialized training program in specimen dissection and obtaining the necessary certification.

The term "the art of grossing" is frequently used because this practice involves much more than a routine task—it carries critical value that shapes the entire specimen analysis process. [40]

Figure 10: Example of kidney tissue grossing.

In fact, the lack of proper sizing, well-defined cutting lines, sampling quality and accurate documentation can create challenges in microscopic analysis, potentially compromising the final diagnosis. «If the dimensions of the specimen are not recorded, the key section not taken, the proper special studies not performed at the time of the initial gross examination, the chances of acquiring this information may be lost forever. In many cases, an inadequate gross dissection and sampling will invalidate the microscopic interpretation». [41]

What situation could be worse than examining a slide that features an incorrect or incomplete depiction of the lesion?!

Grossing procedures involve specific manual skills for granting a quality outcome:

- Prepare uniform, thin slices (up to 5 mm) to ensure consistent and effective tissue processing.
- Handle specimens carefully to prevent damage or trauma.
- Use clean surfaces and tools to avoid cross-contamination between specimens.
- Select representative portions of suspicious lesions to enable accurate diagnosis.

Grossing the tissue facilitates proper penetration of the fixative, ensuring that the fixation process begins effectively. If fixation is not performed correctly, as discussed in the 'Fixation' chapter, it can adversely affect the analytical phase, leading to altered staining and compromising the overall diagnostic process. Therefore, it is vital to meticulously evaluate both the methods of execution, and the tools employed to complete the grossing process.

First and foremost, safety considerations must be prioritized. Specimens, as outlined in the previous chapter 'Specimen Handling,' are typically transported in specifically designed containers with a precise

amount of formalin—a substance known for its significant toxicity [42, 43]—to facilitate the initial fixation process. Then, the specimen must be extracted from the formalin, well described (size, shape, texture, colour, consistency of tissue), sectioned and placed in cassettes to prepare for the processing phase. It is therefore essential for the operator to work in a safe environment to prevent exposure to the toxic fumes of formalin and the risk of contracting pathogenic infections, thus minimizing biological hazards. [17]

Today, in many laboratories, technicians perform grossing on basic cutting boards *(Figure 11)*, simple suction tables, or in cabinets that are unsuitable for this activity as they do not have any extraction system. The ideal setting for performing grossing is within a grossing station, which is designed to provide all the necessary tools for achieving optimal results while ensuring complete safety. Selecting the right grossing station is a crucial aspect, as it involves various features that impact both the laboratory's routine and the technicians' work.

The grossing stations available on the market may be of either chemical or biological nature, depending on the laboratory's activities. While simple chemical hoods or cabinets can shield the operator from harmful fumes, they do not provide protection against biological hazards. In case of biological cabinets, a class (1, 2 or 3) is assigned based on the level of biological protection provided.

In recent years, innovative hoods have been launched in the market to meet both chemical containment regulations and biological safety standards. The advanced extraction systems effectively direct both formalin and biological fumes, preventing their escape from the hood and providing a secure working environment *(Figure 12)*.

The inclusion of specially angled glass shields acts as a physical barrier between the specimen and the operator, effectively containing fumes while also providing splash protection.

Given its essential role in the final diagnosis, grossing must be meticulously documented. Proper

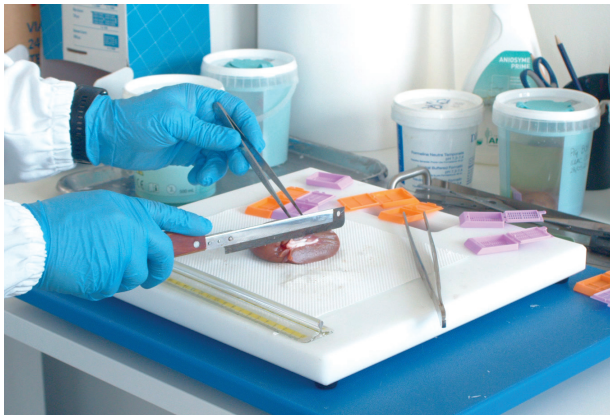


Figure 11. Grossing on basic cutting boards poses significant risks, compromising both the safety of the specimen and the operator, who may be exposed to harmful or biologically infectious substances.

Figure 12. Example of efficient fume extraction.

documentation ensures the traceability of the specimen's journey and helps identify any discrepancies in patient data or errors. That's why the saying goes "A picture is worth a thousand words".

In today's laboratories, technicians recognize the importance of documentation. However, they often lack suitable equipment for comfortably capturing standardized images, making it highly dependent on the operator. Documentation is often conducted in a haphazard, imprecise, and unsafe way, exposing the operator to potential risks *(Figure 13)*. Similarly, there is a high risk of losing files and images, which could compromise the entire diagnosis.

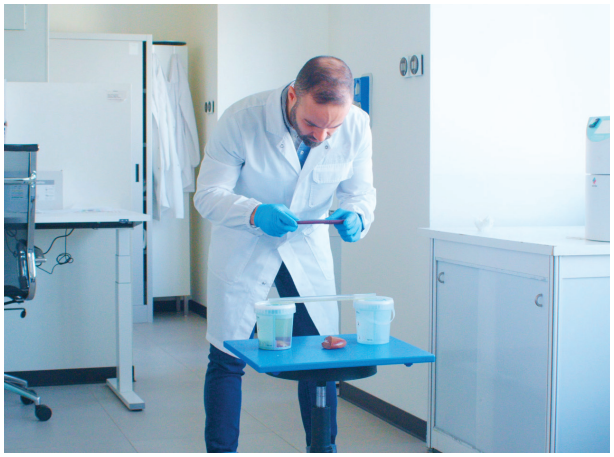


Figure 13. Example of how inadequate equipment forces pathologists/technicians to perform documentation in a dangerous and inefficient way.

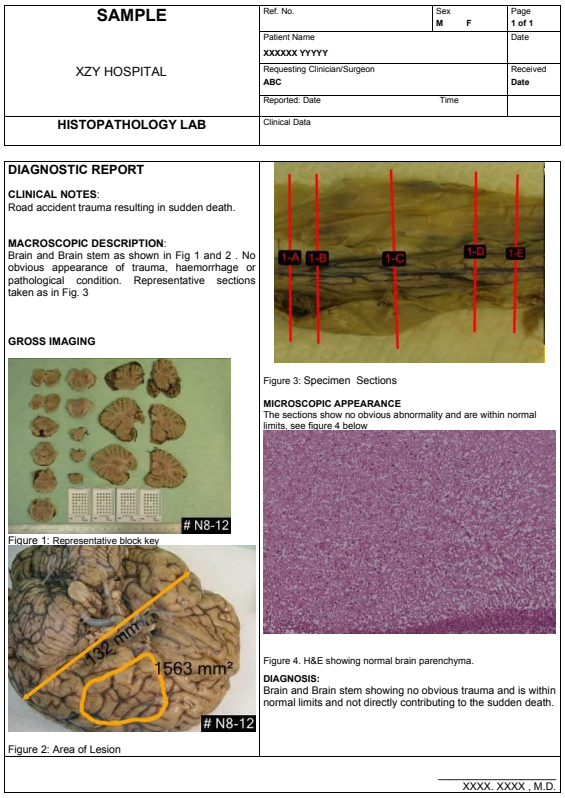


Figure 14. Example of specimen report demonstrating how images and notes enhance the clarity of the specimen description.

It is clear that specialized tools for digital documentation of the grossing process are fundamental. These systems include high-resolution cameras that can be easily controlled through dedicated interfaces for capturing high-definition images and high-resolution videos. They also feature integrated editing tools that provide access to various functionalities, such as estimating sizes and areas, adding notes and creating sections and quadrants to enhance the diagnostic process. These tools also facilitate the creation of a final report *(Figure 14)*, which the pathologist can easily consult later during the diagnosis process. Documentation serves both to validate the procedures performed during grossing and to facilitate training. Images and videos are invaluable resources for teaching new personnel, residents, and junior staff how to excise the appropriate portions of specimens. Additionally, high-resolution images are imperative for submitting cases to journals for scientific publication, as well as for creating image-based reports for clinicians and the entire medical team. [44] This documentation can be live streamed to provide real-time remote guidance for operators in the OR and in the AP department. [45]

Some advanced digital systems are equipped with innovative applications that automate the capturing of biopsy images. This feature streamlines workflow and enhances traceability by automatically creating the case ID folder when the cassette barcode is scanned and saving the captured image within it. As a result, operators can focus on other tasks while the image documentation of tissue preparation is completed automatically, saving time.

Another important feature of the grossing station is its ergonomic design.

The grossing procedure is highly complex and requires precision. For this reason, it must be performed in complete comfort, allowing the operator to choose between standing or sitting, depending on their needs, especially considering the long work shift. Many grossing stations currently available on the market frequently fail to meet the ergonomic standards required by modern laboratories *(Figure 15)*. This often arises from the workspace being challenging to access and the grossing station not easily movable. Additionally, the presence of a vertical protective glass

shield can prevent the operator from getting close enough to the specimen, leading to difficult handling and reducing overall grossing efficiency.

For these reasons, contemporary grossing stations offer an innovative approach, enabling operators to work in an environment that adapts to their needs, rather than forcing them to conform to the constraints of the workspace.

The operators can customize the height of the working area to suit their preferences using an efficient motorized adjustment system. An easily accessible interface allows for the consultation of grossing guidelines and provides control over all system functionalities, including lighting, ventilation and height adjustment. The most advanced grossing systems also feature a sensor that monitors the presence of the operator and automatically activates or deactivates the filters and ventilation system, providing maximum user comfort and reducing energy consumption. Additionally, the introduction of an angled glass shield ensures effective fume containment and splash protection while providing the operator with optimal visibility of the specimen from above during the grossing process. The inclusion of casters enables the grossing station to be easily moved and repositioned within the lab for cleaning or renovation purposes, providing complete flexibility without any restrictions.

Finally, an advantage that should not be overlooked is the ability to organize the working area with a modular approach. Advanced grossing systems offer various modular options that can be rearranged according to the operator's specific needs, such as adjusting the work surface based on personal preferences or the size of the specimen (e.g., colon). Another advantage is the ability to easily transition from a single-operator configuration to a double-operator setup by simply reconfiguring the arrangement of the modules. This adaptability leads to significant cost and space savings by eliminating the need for an additional grossing station while ensuring the optimal configuration is always available.

Once the cassettes are created at the grossing station, it is standard practice to scan them and save the configuration of the batches. This aspect will be further explored in the 'Tracking' chapter.

Figure 15. Example of grossing station that fails to meet safety standards and lack flexibility, making the workspace considerably more uncomfortable.

IT'S TIME TO DO BETTER

Do better now in **specimen grossing**!

Grossing is the foundation of diagnostic accuracy. Milestone, with its modular grossing stations and enhanced macro digital system, ensures operator safety and high-quality imaging, video, voice recording and editing capabilities.

DISCOVER **MILESTONE SOLUTIONS**

UltraGROSS *Modular Grossing Station*

UltraGROSS is an advanced grossing station designed to provide operators with maximum safety, ergonomics, flexibility and digital documentation.

Brochure
Video
Webinar

eGROSS *Ergonomic Mobile Grossing Station*

eGROSS is an updated grossing station engineered to ensure operator comfort and integrate a documentation system for complete specimen traceability.

Brochure
Video
Webinar

WorkSTATION *Workcenter for Small Biopsies*

WorkSTATION is an ergonomic grossing station used for grossing procedures and macro digital documentation of small biopsies.

Brochure
Video
Webinar

DISCOVER **MILESTONE SOLUTIONS**

MacroPATH *Macro Digital Imaging System*

MacroPATH, the exclusive Milestone digital imaging system, easily integrates with all grossing stations for comprehensive documentation during the grossing phase.

Brochure
Video
Webinar

C-Scan *Automatic Cassette Detecting System*

C-Scan option for MacroPATH ensures better workflow and superior traceability through the automatic scanning of cassettes with biopsies.

Brochure
Video

LOOX *Eye-Control for Grossing Documentation*

With LOOX option for MacroPATH, the operator can smoothly perform tasks such as zooming, capturing images and recording videos by simply looking at the command icons on the screen.

Brochure
Video

05.

Tissue Processing

As previously noted, microscopic analysis of cells and tissues requires the preparation of very thin, high-quality sections mounted on glass slides and appropriately stained to demonstrate normal and abnormal structures. Once the grossing step has been completed and the cassettes have been prepared, the specimen is ready for the next phase, which serves as the core of the workflow and represents a fundamental step in the histological process: tissue processing. [46]

Any errors during this step can result in tissue specimens that cannot be sectioned, thus failing to provide useful microscopic information. This can be disastrous, particularly when working with diagnostic human tissue, where the entire specimen has been processed. Without any remaining tissue, no diagnosis can be made, leaving the patient waiting for answers.

The processing phase consists of four main stages:

1. Fixation. As discussed in the previous chapter, fixation usually begins when the specimen is collected. However, there are instances where fixation is incomplete or the specimens are still fresh, in which case the fixation process is carried out directly on the processor. This step aims to preserve the tissue's structure and prevent decomposition. It involves soaking the tissue in a fixative solution, typically 10% NBF (Neutral Buffered Formalin), which cross-links proteins and stabilizes cellular components.
2. Dehydration. After fixation, the tissue is dehydrated to remove water, and this step is typically performed using a series of graded alcohol solutions (sometimes the first step is a mixture of formalin and alcohol).
3. Clearing. This stage involves the removal of the dehydrant used in the previous step and its substitution with a solvent, either aliphatic or aromatic, that is miscible with both alcohol and the embedding medium. The most common clearing agent in AP labs is xylene, which is highly toxic. However, today, there are effective alternatives to this approach through the use of greener solvents.
4. Wax infiltration. The tissue is then infiltrated with molten paraffin wax, which replaces the clearing agent and provides initial support for sectioning, finalized during the embedding phase.

Figure 16. Examples of incorrectly processed specimens.

Each stage plays a crucial role in processing and, if not properly controlled, can affect the final quality of the specimen and, consequently, the final diagnosis.

For example:

- Incomplete fixation of the tissue can result in poor preservation of cellular structures, while over-fixation, though rarer and less harmful, can cause DNA fragmentations, deamination of bases, antigen masking,leading to inconsistent molecular and immunohistochemistry assays.

- Under-dehydration makes the tissue too soft and macromolecules prone to hydrolysis, while over-dehydration can make tissues too hard and brittle.
- Inadequate clearing can prevent proper fat clearing and make paraffin impregnation impossible, while over-clearing can lead to protein denaturation.
- Improper infiltration results in incomplete paraffin sections during the microtome step, resulting in holes in the slide.

The first significant innovation in the field of tissue processing occurred at the beginning of the 20th century, when the transition was made from manual to automatic processing. This shift was marked by the invention of the first automatic tissue processor, created by Arendt in 1909. From that moment on, the procedure underwent no major technological advancements and remained essentially unchanged for almost a century, until the advent of hybrid processing dramatically transformed this step. [47, 48] This innovation made tissue processing faster, aligning with the need for higher-performance instruments and advancing patient care by enabling 'same-day diagnosis'. Milestone has introduced modern tissue processors that incorporate this technology to improve quality, personnel and specimen safety, while implementing a lean workflow to improve laboratory productivity and workload management. This methodology uses short runs throughout the day for thin specimens and biopsies, while reserving longer processing times for thicker and fatty tissues overnight, effectively transforming idle daytime hours into productive ones. [49, 50] In many cases, the presence of a dual cavity further supports this strategy by allowing the simultaneous running of two processes, thereby enabling continuous specimen loading *(Figure 17)*.

Another important factor affecting processing efficiency is the ease of reagent management. Replacing reagents is often a time-consuming and cumbersome task, requiring operators to manually transfer reagents while exposing themselves to potential risks. To address this, Milestone's dual retort processors have introduced an additional paraffin reservoir that enables automatic

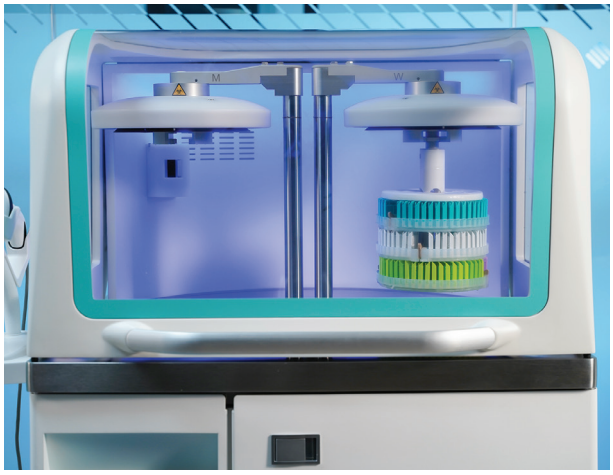


Figure 17. Example of dual cavity tissue processor.

replacement of paraffin without interrupting ongoing protocols. Moreover, reagents are supplied in standard 5-litre or 1-gallon containers, allowing operators to directly replace the entire container and simplify the process.

During the processing phase, it is crucial to ensure the specimen is handled with utmost safety to preserve its integrity and maintain its quality. Advanced tissue processors are designed to offer a wide range of protocols tailored to the specific type of specimen being processed, ensuring optimal results for every application [36,37]:

- Fast programs for efficiently handling small and urgent biopsies.
- Extended programs for processing larger specimens.
- Specialized protocols for fatty tissues.

Additionally, the processing programs should be user-friendly, allowing operators to easily edit and customize the protocols to meet specific requirements.

Selecting the correct protocol is only one part of the process; continuous monitoring is critical to effectively address potential failures. Reliable tissue processors feature automatic safety mechanisms to protect specimens in the event of electrical faults during processing. In addition, modern systems are equipped with advanced technological innovations, such as components that separate alcohol-based circuits from

water-based ones to prevent cross-contamination and protect the specimens. Integrated sensors further enhance reliability by monitoring critical parameters, such as reagent purity, and providing precise information on when replacement is required. This information is also significant from an economic perspective, as it allows for reagent replacement only when necessary, minimizing reagent waste and reducing overall laboratory costs.

Equally vital is the integration of an automatic notification system that promptly alerts the operator to any malfunction, enabling immediate intervention to minimize disruptions and maintain process efficiencies. Human error can play a significant role in compromising the success of processing, so it must be minimized by implementing proper technological solutions. For example, mistakes during reagent replacement or lapses in handling cassettes can disrupt the workflow and affect results. This is why traceability has become a cornerstone of modern laboratory operations. [51] The latest Milestone generation systems are equipped with a robust barcode-based tracking system that provides full visibility of the workflow. This includes knowing the exact location of a case, how it was processed, the exposure times and temperatures of the specimen to various reagents and maintaining a detailed log of reagent replacements.

No less significant are the aspects related to operator safety *(Figure 18)*. It is imperative for operators to use non-hazardous reagents, such as isopropanol, instead of xylene, and to minimize direct exposure to these substances. The use of isopropanol as a substitute for xylene also offers significant economic benefits, as it extends the lifespan of the wax and reduces the need for frequent wax changes, since it can be easily cleaned with special cycles.

This goal is further supported by advanced equipment designs, such as fume extraction systems that can be connected to a central laboratory ventilation system or equipped with filters to prevent the emission of harmful vapours.

These features ensure proper ventilation both in the workspace and within drawers. Additionally, the use of commercial tanks, as previously mentioned, eliminates the need for risky manual refilling, thereby further enhancing operator safety.

Figure 18. The safety of the operator is paramount during the specimen processing.

IT'S TIME TO DO BETTER

Do better now in **specimen processing**!

Tissue processing is the heartbeat of every pathology lab, and Milestone's tissue processors set new standards with continuous batch loading, wax transfer elimination, turnaround time reduction, maximized productivity, and enhanced safety.

DISCOVER **MILESTONE SOLUTIONS**

MAGNUS *High Throughput Tissue Processor*

MAGNUS is an automatic tissue processor designed for continuous loading with dual retorts and robotic arms, eliminating downtime and cleaning cycles

Brochure
Video
Webinar

LOGOS EVO *Advanced Tissue Processor*

LOGOS EVO is an advanced tissue processor with dual retorts, resulting in faster processing and enhancing laboratory workflow through dual run mode

Brochure
Video
Webinar

DISCOVER **MILESTONE SOLUTIONS**

LOGOS One EVO *Smart Tissue Processor*

LOGOS One EVO is a smart traditional tissue processor with dual retorts, optimizing workflow efficiency through dual run mode.

Brochure
Webinar

KOS *Multifunctional Tissue Processor*

KOS is a multifunctional microwave processor, designed to be highly compact for small laboratories and suitable for a wide range of applications

Brochure
Video
Webinar

06.
Embedding

After the specimen has been properly processed, it moves on to the next step: embedding. During embedding, the operator places the specimen into the embedding medium and allows it to solidify, preparing it for sectioning at the microtome. A variety of embedding media can be used, with paraffin being the most commonly chosen. This step is usually performed manually using steel moulds, into which hot paraffin is poured *(Figure 19)*. [52]

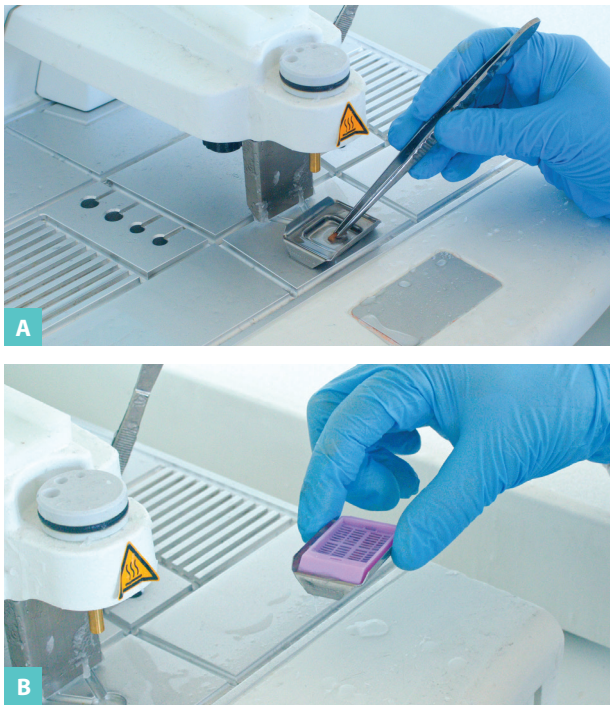


Figure 19. A) The specimen is carefully placed inside the mould, oriented using forceps and then filled with paraffin. B) The cassette is placed on top of the specimen, filled with more paraffin if necessary, and then transferred to the cold plate.

The embedding step is typically managed using dedicated workstations, which are equipped with all the necessary modules to carry out the different stages of embedding:

- Thermal module, designed to maintain the cassettes with paraffin-infiltrated specimens at a warm temperature after removal from the processor, while awaiting their turn to be embedded.
- Dispensing module, designed to dispense paraffin through a dedicated valve connected to a reservoir of ready-to-use, melted paraffin.
- Cold module, used for positioning and cooling the moulds in which paraffin has been poured, enabling it to solidify.

Modern systems are highly flexible, featuring separate modules that allow the operator to position them as needed according to their workflow. They are also compatible with all types of cassettes.

To further enhance specimen safety, Milestone introduced a tracking system that allows for visual verification of the specimen's preparation during the grossing step.

The embedding step is a common bottleneck for most labs. It is well known that this manual process, repeated across numerous cassettes, can be both monotonous and physically demanding.

It is estimated that the average time spent on each cassette is significant (around 1 minute per cassette). Clearly, the embedding phase functions as a bottleneck in the laboratory, as it demands considerable time and, crucially, resources that must be entirely devoted to this task.

Moreover, like all manual tasks, it is highly operator-dependent, which leads to a lack of standardization in

the process, potentially impacting the outcome of the final diagnosis.

New technologies and innovations enable to address these issues, so the time to do better is now. For these reasons Milestone has developed automated embedding systems. These systems are integrated directly into the processor, acting as a seamless part of the final wax impregnation phase. They represent a completely new and revolutionary concept, featuring a custom-designed rack along with its specialized accessories. During the processing phase, the rack can adjust the cassettes to different optimal orientations for each stage. An angled position ensures the smooth flow of reagents throughout the process, while a horizontal position facilitates optimal paraffin filling within the cassette. The operator ensures the proper orientation of the specimen during the grossing phase by placing it on specially designed sponges. These sponges firmly hold the specimen in place during processing, preventing excessive compression and ensuring smooth handling during sectioning.

This automatic method reduces specimen handling, as the specimens are loaded into the tissue processor and extracted already embedded in paraffin, helping to preserve their integrity [53] *(Figure 20)*.

The workflow becomes more streamlined and efficient, eliminating the typical downtime between the removal of specimens from the processor and the start of embedding. Moreover, this approach greatly improves laboratory efficiency by freeing up personnel from the tedious manual embedding task, allowing them to focus on added value activities. [53,54]

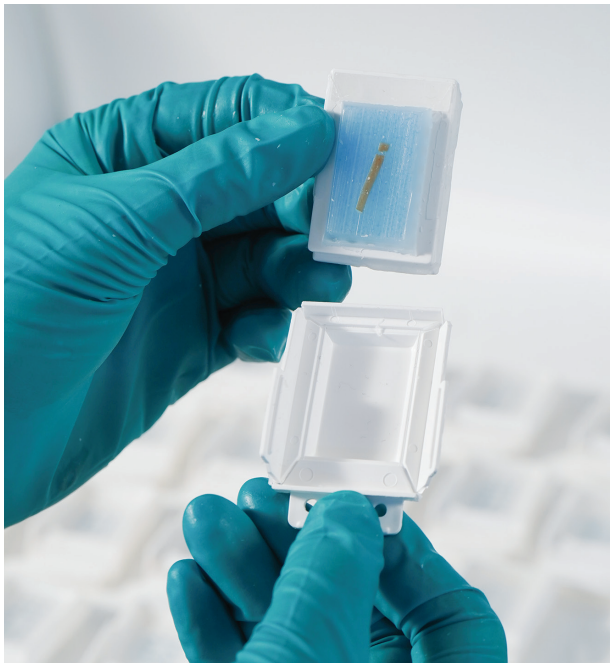


Figure 20. Example of a block obtained through an auto embedding process.

IT'S TIME TO DO BETTER

Do better now in **specimen embedding**!

Embedding is a critical bottleneck in the histology world. Milestone's automated solution integrates embedding directly into the processing step, optimizing and standardizing the entire workflow.

DISCOVER **MILESTONE SOLUTIONS**

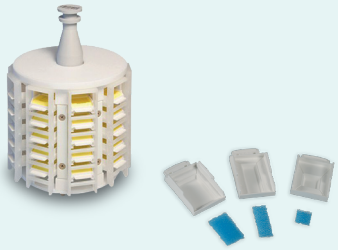
HistoDream EW *Embedding Workstation with Biospecimen Traceability*

HistoDream EW is an ergonomic and modular embedding workstation that allows for customization of the embedding workflow to suit the operator's needs.

Brochure

SYNERGY *Auto-embedding System: Processing + Embedding All-in-One*

SYNERGY is a revolutionary patented rack system which enables users to automatically embed tissues as a part of processing protocols.



Brochure

Video

Webinar

07.

Cutting

During the cutting phase, the processed specimen enters the phase where it will be finely sectioned and mounted on a glass slide. This step is necessary to prepare the tissue for staining, immunohistochemistry, and molecular analysis, ultimately leading to the final diagnosis. The cutting process is performed using a microtome *(Figure 21)*, which slices the paraffin-embedded tissue block into thin and precise sections. This highly delicate and technical procedure relies heavily on the skill and expertise of the technicians. [55] The main challenge at this stage is to produce a consistent ribbon of sections that is free of artifacts.

Figure 21. Example of microtome sectioning.

A microtome is a scientific instrument designed to cut extremely thin tissue slices, typically ranging from 2 to 10 µm in thickness, enabling the examination of inner sections of individual cells.

The paraffin-embedded tissue block is first cooled below freezing, then mounted onto the microtome clamp to ensure it is securely fixed in place. A sharp razor blade, meticulously aligned at the optimal angle to the block, slices through the paraffin with precision, while the microtome mechanism advances the block in controlled, incremental steps, generating a thin, flawless ribbon of sections. The ribbon is carefully lifted from the knife and gently placed onto a cold-to-warm water bath, allowing it to flatten *(Figure 22)*.

Figure 22 - Example of high-quality ribbon in water bath.

Individual sections are then adhered to glass slides, prepared for staining, and subsequently sent to pathologists for microscopic examination.

Microtome sectioning is a fundamental step in histology, focused on producing high-quality sections for microscopic examination. This process demands a careful balance of key factors, including tissue hardness, knife sharpness and angle, block orientation, temperature, and microtome settings. Mastering these variables is essential to ensure accurate, consistent, and reliable results.

In addition to these variables, as previously emphasized in the 'Grossing' chapter, it is crucial to recognize that this step depends significantly on the proper execution of the grossing phase.

During tissue grossing, the operator must meticulously select the correct portion of the suspicious mass. If this step is overlooked or performed incorrectly, even flawless sectioning, optimal staining, and meticulous diagnosis will not prevent misleading results for the patient—since the target tissue may have been missed or neglected.

Microtomes originally emerged as fully mechanical sled-type models, which, in practical terms, cut the paraffin block using a horizontal movement, with entirely manual adjustments.

Today, common laboratory setups include rotary semi-automatic motorized microtomes, requiring minimal operator intervention. Fully automated robotized microtomes are also available; in this case operators primarily assist the machine by loading paraffin blocks and unloading paraffin sections that have already been mounted on glass slides.

The advancement of automation not only frees operators from the manual, tedious, and stressful task of block cutting but also optimizes laboratory workflow, saving valuable time and resources during the cutting phase. Moreover, it guarantees consistent, high-quality, and standardized results across all specimens, eliminating the variability and drawbacks associated with operator-dependent processes.

Another essential aspect is the protection of the operator. For example, Milestone does better by adopting various safety features in its microtomes, such as blade covers when not in use and mechanisms that halt the microtome's operation if necessary. To further enhance the cutting process, its microtomes are paired with specialized devices that generate an ionized flow to neutralize electrostatic charges, which are often responsible for producing weaker, sticky, or wrinkled sections. By addressing this issue, these devices ensure the production of higher-quality sections while enabling operators to work more efficiently, streamlining the cutting process, and improving overall productivity.

IT'S TIME TO DO BETTER

Do better now in **specimen cutting**!

Cutting histological tissue demands advanced tools to ensure high-quality sections, safeguard technicians, and optimize workflow. Milestone's solutions are specifically designed to tackle these challenges, providing a reliable and efficient approach to sectioning.

DISCOVER **MILESTONE SOLUTIONS**

HistoDream M *Semi-Automated Microtome*

HistoDream M is a semi-automatic microtome designed to deliver high-quality sections while prioritizing operator safety during cutting procedures.

Brochure
Video
Webinar

HistoDream AM *Automated Microtome*

HistoDream AM is an advanced automatic microtome that ensures precise and safe sectioning, while accelerating the cutting process and enhancing laboratory workflow efficiency.

Brochure
Video
Webinar

EasyCUT *Static Charge Remover for Microtomes*

EasyCUT neutralizes electrostatic charges during the cutting phase, aiding technicians in achieving perfect, non-sticky and wrinkle-free ribbons.

Brochure
Video
Webinar

08.
Staining

The effort invested by the laboratory team in processing specimens culminates in the final step before sending slides to pathologists for diagnosis: tissue staining. This process enables the identification of cell shape and structure under a microscope (nowadays, typically digital), allowing for the evaluation of whether tissue physiology is preserved or altered. [56, 57]

Histology employs a diverse array of stains, including dyes, metals, labelled antibodies, and fluorophores. Sometimes, it is necessary to identify specific cells and tissue components that routine stains like haematoxylin and eosin (H&E) cannot differentiate. This is where special stains come into play *(Figure 23)*. There are dozens of them, each designed to identify altered functions by targeting specific components, such as glycogen, mucus, fibers, pigments, and the extracellular matrix.

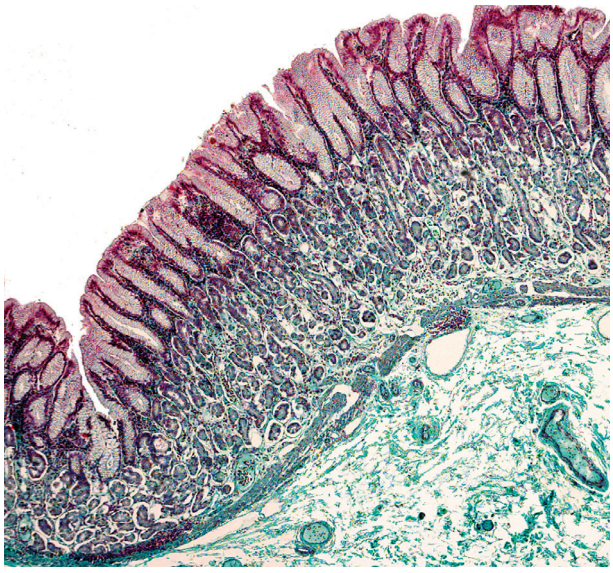


Figure 23. Example of special stain. Gastric mucosa stained with the Masson trichrome stain showing: surface epithelium, gastric pits with foveolar cells, fundic glands and muscularis mucosae.

Immunostaining in histology is a relatively recent technique used to detect specific proteins in cells and tissues through a biochemical reaction with antibodies. These antibodies bind to specific antigens—proteins that may exhibit upregulated or downregulated transcription in cells and tissues where normal physiology has been altered, typically in pathological conditions such as dysplasia, metaplasia, and neoplasia. The antibody-antigen binding is made visible through various chromophore signals. This technique is widely used not only for diagnosing diseases but also in medical research to study the structure and function of cells and tissues, as well as in the development of new treatments. Nonetheless, immunostaining is a powerful and sensitive technique that assists pathologists in accurately classifying tumours, thereby enabling personalized treatment strategies.

This technique is now largely automated with stand-alone systems that can perform multiple stains simultaneously, streamlining laboratory workflows, reducing response times, and monitoring personnel and resource costs. The process automation ensures greater standardization, which enhances the overall quality of diagnosis. Moreover, modern automatic stainers prioritize operator safety by incorporating advanced safety features, such as sensors that detect potential procedural errors, and an enclosed design equipped with filters and connections to the laboratory's ventilation system, which effectively capture and manage the toxic fumes generated by the reagents.

Looking ahead, pathology is increasingly moving towards more analytical assays, such as the molecular and genetic profiling of tissues. Molecular analysis *(Figure 24)*, as a companion diagnostic test, provides more specific, sensitive, and accurate methods that

enhance diagnostic precision.
Molecular test enables data-driven diagnoses, allowing for disease sub-typing based on a unique case footprint. However, classical staining continues to be a cornerstone of the diagnostic process.

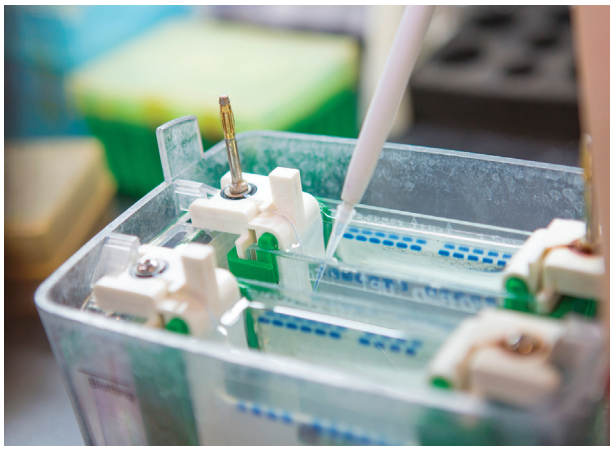


Figure 24. Example of molecular analysis (Western blot for protein detection).

09.

Tracking

Implementing traceability is crucial for decreasing the number of errors occurring in a laboratory, thereby ensuring patient safety. Each specimen is unique and irreplaceable, and even a single small error can compromise the entire diagnosis. [51]

Tracking means having full visibility into a specimen's long journey *(Figure 25)*, from the operating room to the pathologist's desk for diagnosis. Along the way, errors can occur at several points, especially due to the manual nature of some procedures.Tracking ensures immediate access to all relevant information whenever needed. [58] This data is also essential for gaining deeper insights into laboratory operations, enhancing efficiency, streamlining workflow, and optimizing time management. Prior to discovering the possible improvements that can be done, we have identified the potential error points throughout the specimen's journey.

OVERVIEW OF TODAY'S SITUATION

» Specimen Collection

The main issues that arise during this phase include communication errors, which can lead to mismatches between the specimen and the requisition form, or labelling mistakes on the specimen's container.

A study estimated that approximately 4.3‰ of surgical specimens are affected by identification errors, including unlabelled specimens, empty containers, incorrect laterality, wrong tissue site or patient, missing patient name, or absent tissue site. [59]

» Transportation and Accessioning

Transport conditions are crucial for determining whether a specimen has been properly preserved, including factors such as transport time and temperature. Missing information of this kind can potentially compromise the specimen's integrity and the reliability of subsequent analyses.

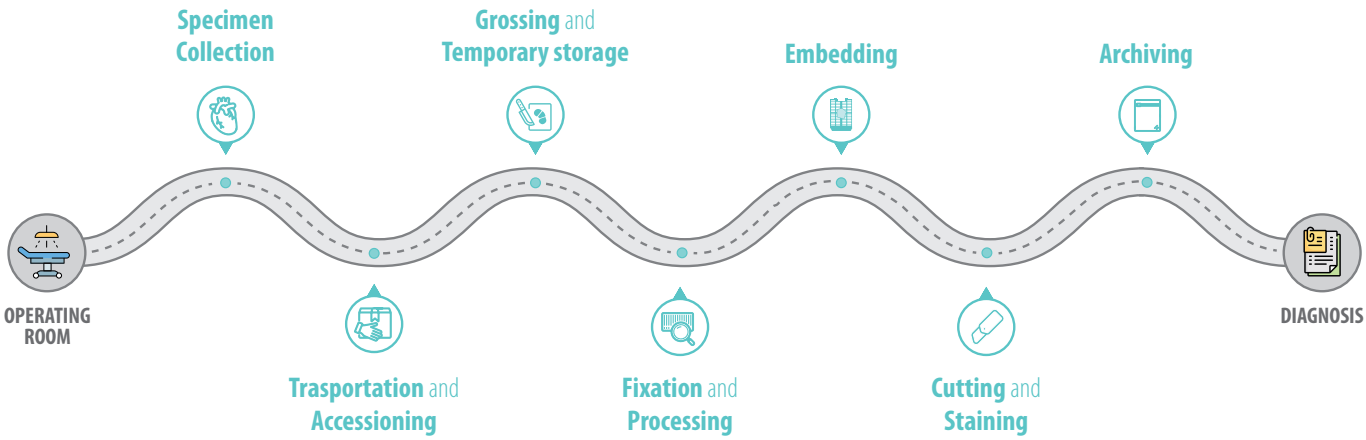


Figure 25. The complete journey of a specimen, from the operating room (OR) to the final diagnosis.

Once the specimen arrives at the laboratory, it enters the accessioning phase, where it is carefully checked. However, errors can occur during this process, which can include specimen/code mismatches, incorrect labelling and patient misidentification errors.

» Grossing and Temporary Storage

During the grossing phase, the information on the requisition form is manually compared with the details on the container, including patient identification, tissue type, and the number of containers. If any data doesn't match, time is spent identifying the error, which disrupts the laboratory workflow and delays the entire process, ultimately affecting the timely delivery of the diagnosis.

Furthermore, the lack of digital systems to document the specimen, grossing procedures, measurements, and annotations can result in a substantial loss of information. Errors can also occur during cassette preparation, especially when the code is written manually. Printed materials help minimize errors by ensuring that each case is managed correctly.

During temporary storage, when the specimen can be recalled for reworking and further diagnostic validation, it re-enters the main process. Once again, checkpoints and tracking ensure error-free operations.

» Fixation and Processing

Optimal tissue preparation must consider fixation time and conditions: these parameters are only available if proper tracking of each specimen is in place. Exceeding or failing to reach the minimum fixation time impairs both immune reactivity and molecular material retrieval. Moreover, during tissue processing, a cassette may be lost either during processing or while being transferred from the grossing area to the processing area or from the processor to the embedding zone. Therefore, it is essential to have tracking checkpoints that ensure the presence of cassettes at each step, using professional tools to minimize material loss.

» Embedding

Small biopsies are the most susceptible to being lost. A common error in high throughput labs is that they may remain stuck to the lid of the cassette and be accidentally discarded. This issue often goes unnoticed, especially when the number of specimens in the cassette isn't properly tracked, counted, or documented. The ability to review images from the grossing phase using a digital system helps reduce the risk of tissue loss or oversight, allowing the operator to quickly address potential issues.

» Cutting and Staining

The cassette and, consequently, the slides share the same code as the processed case. If this code is incorrect or the printed slide is mixed up, the tissue may undergo improper staining. Similarly, both slides and paraffin blocks can be misplaced or lost, resulting in delays that jeopardize the diagnostic process. Also there, the possibility to review images from the grossing phase acts as an additional check point.

» Archiving

Archive errors are also common. The increasing availability of automatic archiving systems for both slides and cassettes helps prevent misplacement and retrieval issues.

AVAILABLE SOLUTIONS

Now that we have gone through the specimen journey, let's evaluate the approaches to address these issues. As stated above, it is evident that errors can occur at every stage of the process. When these mistakes accumulate, they can create a domino effect, with each error amplifying the next. Labs can't wait to address these issues, as the time to do better is now. Milestone enables labs to implement both hardware and software tools, capable of capturing as much information as possible at each step and securely storing it, allowing for the precise and accurate reconstruction of the specimen's journey and providing helpful information for the diagnosis.

» Hardware Solutions

As already discussed in previous chapters, the presence of instruments capable of collecting information about the specimen at each step is crucial:

- At specimen collection, automatic systems are needed to document the collection step and control formalin dispensing.
- During transportation, tools that monitor travel conditions (time and temperature) are critical.
- In the accessioning phase, instruments that capture label images and information are required.
- During the grossing step, macro digital imaging systems should be used for enhanced documentation.
- Once the cassettes are created at the grossing station, it is standard practice to scan them and save the configuration of the batches. However, this process can lead to various errors, such as incorrect codes, duplicate codes, or codes that are not read accurately. Advanced systems have been introduced to the market at the hardware level, capable of replacing manual tracking of cassettes during both the pre- and post-processing stages, thereby enhancing both efficiency and accuracy. These systems are equipped with cutting-edge, precise technology *(Figure 26)* that automates the scanning process, eliminating potential errors typical of manual tracking. Additionally, they reduce the workload on staff, enabling them to focus on other critical tasks.

Figure 26. Example of an automatic tracking system.

- In the fixation and processing phases, all processing parameters should be recorded and saved. Tracking systems can also be utilized after processing as a verification tool to ensure that all cassettes previously registered in the batch have been processed correctly and have not been misplaced, through a simple batch comparison function.
- During the embedding, cutting, staining, and archiving steps, it is essential to verify the specimens and ensure they match the grossed specimen by consulting the documentation collected.

» Software Solutions

From a traceability standpoint, across the entire specimen workflow—from collection to diagnosis—Milestone has developed and introduced a software solution to the market: MileWATCH.

This platform, which maintains continuous connections with all laboratory instruments, serves as central repositories for information. It not only collects and stores critical data at every stage of the process but also ensures seamless integration between various instruments, providing a comprehensive, real-time overview of the specimen's journey and ensuring its accuracy throughout. This software solution, in constant connection with the LIS, allows for the transfer of data and provides access to this information whenever needed. It also allows real-time monitoring of various instruments, keeping users informed about any potential issues that may arise during the day. By receiving timely notifications *(Figure 27)* about these problems, users can take immediate action, ensuring quick resolution and preventing disruptions to the workflow and securing the specimen safety. The recording and analysis of laboratory activities are also an excellent way to identify potential bottlenecks and reorganize workflows in a more efficient and effective manner, optimizing staff tasks, time, and costs.

In today's healthcare environment, traceability has become a crucial component of the patient care process. The accurate recording and matching of all specimens with their corresponding documentation are essential to ensuring the integrity of diagnostic workflows. [4] This practice is one that laboratories can no longer afford to overlook.

Figure 27. Operator receiving MileWATCH notifications.

IT'S TIME TO DO BETTER

Do better now in **specimen tracking**!

Milestone believes that traceability is a core value for improving specimen safety and optimizing workflow management, utilizing tools that provide comprehensive documentation at every step.

DISCOVER **MILESTONE SOLUTIONS**

MacroPATH *Macro Digital Imaging System*

MacroPATH, the exclusive Milestone digital imaging system, easily integrates with all grossing stations for comprehensive documentation and tracking during the grossing phase.

Brochure
Video
Webinar

C-Scan *Automatic Cassette Detecting System*

C-Scan option for MacroPATH ensures better workflow and superior traceability through the automatic scanning of cassettes with biopsies.

Brochure
Video
Webinar

V-Tracker *Automatic Vial Scanner*

V-Tracker is an automatic tracking system that collects details and information from the specimen's container through a 360° image during the accessioning step.

Brochure
Video
Webinar

DISCOVER **MILESTONE SOLUTIONS**

T-Tracker *Automatic Basket Scanner*

T-Tracker, an automatic basket scanner, automates manual cassette scanning after batch creation, ensuring reliable tracking and detecting any missing codes before and after processing.

Brochure
Video
Webinar

R-Tracker *Automatic Rack Scanner*

R-Tracker is the automatic rack scanner designed to automate cassette scanning for Milestone racks after batch creation, guaranteeing accurate documentation before and after processing.

Brochure
Video
Webinar

MileWATCH *24/7 Tracking and Monitoring*

MileWATCH is Milestone's tracking and monitoring system that traces specimen's journey from the OR through AP, ensuring complete chain of custody.

Brochure
Video
Webinar

10.
Sustainability

Sustainability is an increasingly critical topic in today's world *(Figure 28)*, playing a vital role in preserving our planet and improving our overall quality of life. It deeply influences the choices we make, the way we behave, and how we approach our professional and personal responsibilities, fostering long-term well-being for both current and future generations.

Pathology laboratories, like most medical facilities, face numerous critical challenges daily, one of the most significant being the safe management and disposal of toxic reagents.

Figure 28. A key objective is to optimize the laboratory work environment by developing safer, more sustainable reagents and accessories

These substances cannot be carelessly released into the environment, as they pose serious risks to both human health and ecological systems. Instead, they must be meticulously handled and disposed of in accordance with strict safety regulations and environmental guidelines. There are some improvements that can be made, and our motto "It's time to do better" comes into play here as well! Milestone is committed to develop and introduce innovative tools aimed at reducing or eliminating the use of formalin. As already seen in 'Specimen Collection and Transportation' chapter, instead of relying on formalin, these systems utilize vacuum-sealed, temperature-controlled preservation for specimens whenever feasible. In cases where formalin is necessary, the systems are designed to minimize its usage, carefully calibrating the amount of formalin based on the specimen's weight to ensure the smallest possible quantity is used. This approach not only eliminates or reduces the amount of formalin that needs to be disposed of, thereby lowering the associated environmental and safety risks, but also significantly minimizes the potential hazards to the operator, as we have thoroughly examined the dangers posed by this reagent.

Another area of significant investment is tissue processing, where the goal is to introduce eco-friendly reagents and develop protocols that not only ensure the highest quality results but also optimize reagent usage. In the case of paraffin, Milestone tissue processors don't need any cleaning cycle because the presence of a dedicated wax cavity eliminates the need to transfer wax into the main cavity, preventing issues associated with wax clogging. In the case of other tissue processors, when wax is combined with alternative green reagents, it can be more thoroughly cleaned. As a result, its use can be extended over multiple cycles, eliminating the risk of toxic reagent residues lingering inside and interfering with the integrity of subsequent processes, while also saving on the cost of frequent replacements.

In the grossing area, grossing stations have been equipped with modern sensors capable of detecting

the presence of the operator and based on that, activating or deactivating lights and aspiration as needed. This ensures better resource management in terms of energy, as it prevents unnecessary waste—for instance, if the operator is engaged in other tasks and does not need to worry about managing these functions.

In the field of embedding, the integration of automated systems that perform embedding directly within the processor enhances material efficiency and streamlines workflow. This advanced technology, leveraging specially designed sponges, enables multiple specimens to be securely arranged on the same support in an organized and stable manner, effectively preventing loss during the various stages of the process *(Figure 29)*.

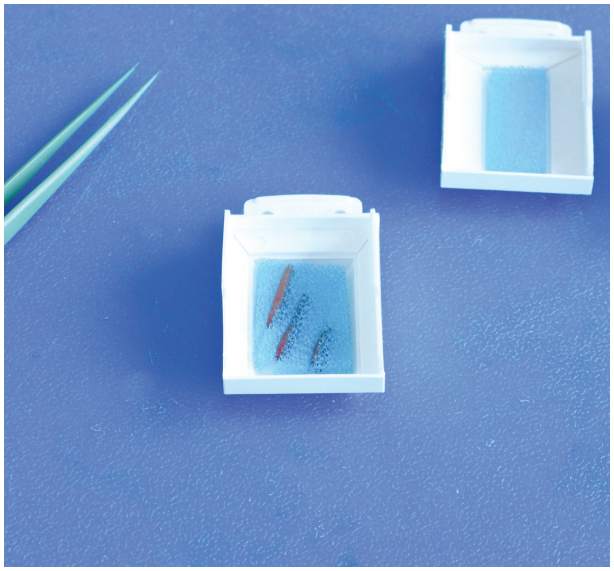


Figure 29. Optimizing consumable usage by organizing multiple specimens on a single sponge.

This, in turn, reduces the number of cassettes that need to be processed, optimizing reagent usage throughout the entire procedure. As a result, this efficiency also extends to the subsequent stages of sectioning and staining, where less material is required, since staining is performed on a smaller number of slides.
Significant progress has been made, but there is still much more we can do. Living responsibly within our environment is not just a choice—it's a necessity. We cannot afford to overlook its importance. We are determined to do better—because the future depends on it!

IT'S TIME TO DO BETTER

Do better now in **reagent choice**!

Milestone is committed to enhancing the laboratory work environment by developing safer and greener reagents, for offering the best histological results while minimizing resource consumption.

DISCOVER **MILESTONE SOLUTIONS**

FineFIX *The Formalin Substitute*

FineFIX is a patented, formalin-free, water-based concentrate fixative. When mixed with ethanol, its low-toxicity additives address the limitations of pure ethanol or ethanol-based fixatives.

Brochure

MileONE *Dehydration Solution for Tissue Processing*

MileONE is a Milestone alcohol-based solution designed to enhance dehydration and lipid extraction while reducing the risk of excessive drying and tissue hardening, offering a superior alternative to traditional ethanol solutions.

Brochure

MileTWO *Clearing Solution for Green Tissue Processing*

MileTWO, a xylene-free solution, ensures optimal preservation of fat cell integrity and maintains nuclear and cytoplasmic morphology during the clearing step.

Brochure

DISCOVER **MILESTONE SOLUTIONS**

JFC Solution *High Performance Xylene-Free Processing Solution*

JFC Solution enables simultaneous dehydration and clearing in a single step, offering a significant advantage over conventional processing methods.

Brochure

MileGREEN *The Xylene Substitute*

MileGREEN is designed to replace xylene in both the clearing and mounting processes. It eliminates the drawbacks of xylene while ensuring optimal structural preservation of fat cells, as well as maintaining nuclear and cytoplasmic morphology.

Brochure

MoL-DECALCIFIER *EDTA Based Decalcifying Solution*

MoL-DECALCIFIER is an innovative, unbuffered 10% EDTA solution that, when combined with elevated temperature and stirring, enables the fixation, decalcification, and processing of bone marrow within 48 hours.

Brochure

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