REPUBLIC OF CAMEROON
PEACE-WORK-FATHERLAND

MINISTRY OF HIGHER EDUCATION

THE UNIVERSITY OF YAOUNDE I

FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

REPUBLIQUE DU CAMEROUN
PAIX-TRAVAIL-PATRIE

MINISTERE DE L'ENSEIGNEMENT SUPERIEUR

UNIVERSITE DE YAOUNDE I

FACULTE DE MEDECINE ET DES SCIENCES BIOMEDICALES

DEPARTMENT OF MORHOLOGICAL SCIENCES AND MORBID ANATOMY

Validation of Digital Pathology Images for Histopathological Diagnosis of Breast Tissues in a Resource-Limited Setting

Thesis written and publicly defended in partial fulfillment of the requirements

for the award of the Medicinae Doctor (MD) degree by

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Academic Year: 2023-2024

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DEDICATION

This piece of work is dedicated to my beloved parents;

Mr. TARLISHI OLIVER YINYU, Mrs. NCHANJI VICTORINE MBONG and Mrs. TARLISHI FRIDA NTASEH

ACKNOWLEDGEMENTS

I would like to thank my Lord and Savior Jesus Christ for his abundant grace and merci that has sustained me all through my days of medical training and has crowned with this piece of work.

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- L = Lecturer

THE PHYSICIAN'S OATH

[Declaration of Geneva adopted by the Geneva Assembly of the World Medical Association in Geneva, Switzerland, September 1948 and amended by the 22nd World Medical Assembly, Sydney, Australia (August 1968)].

On admission to the medical profession:

I will solemnly pledge myself to consecrate my life to the service of humanity

I will give my teachers the respect and gratitude which is their due

I will practice my profession with conscience and dignity

The health of my patients will be my first consideration

I will respect secrets confided in me, even after the patient has died

I will maintain by all the means in my power the honour and noble traditions of the medical profession

My colleagues will be my brothers

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient

I will maintain the utmost respect for human life from the time of conception, even under threat I will not use my medical knowledge contrary to the laws of humanity

I make these promises solemnly, freely and upon my honour.

SUMMARY

BACKGROUND: Whole slide imaging has been used most especially in the field of education, research and in consultations for second opinions. Many studies have been carried out to assess its use as tool for primary diagnosis in pathology. The use of whole slide imaging for breast tissue can be beneficial especially in situations where there are shortages of pathologists. However, there is limited data on the usage of whole slide imaging for histopathological diagnosis of breast tissue in resource-constrained settings. The aim of this study was to assess the possibility of using DP as a diagnostic tool alleviate the multiple the multiple challenges faced with the precocious diagnosis of breast cancer and to provide more evidence to support the implementation of DP in our setting.

OBJECTIVE: To determine the validity of Whole slide imaging for primary histopathological diagnosis of breast tissue specimens.

METHODS: This was a diagnostic, descriptive case control study carried out at the Gyneco-Obstetric and Pediatric hospital and Centre Pasteur Cameroon. This study was carried out for a period of 09 months, extending from October 1st 2023 to June 2024. After obtaining ethical and administrative approvals we retrieved breast tissue glass slides with hematoxylin and eosin stains from the archives of the pathologic departments of the 02 study hospitals. The glass slides were then evaluated by participating pathologist by conventional microscopy. The glass slides were then de-indentification, digitalized and reviewed remotely after a wash out period of 4 weeks.

RESULTS: The intra-observer concordance rates between whole slide imaging and conventional microscopy in the identification of a pathologic process and final pathologic diagnosis were 95% and 70% for respectively. The inter-observer concordance rates between CM and gold standard diagnosis were 93.3 and 63.3% in the identification of a pathologic process and final pathologic diagnosis respectively. The inter-observer observer concordance between WSI and gold standard diagnosis were 95% and 61.7 for identifying pathologic processes and final pathologic diagnosis respectively. The intra-rater agreement of 0.49 and inter-rater agreement of 0.01 and 0.02 for CM and WSI in the identification of a pathologic process. We obtained a 98.2% sensitivity, 33.3% specificity, 96.6% positive predictive value, 100% negative value and area under ROC of 0.151.

CONCLUSION: The intra-rater and inter-observer agreement was moderate and slight. The diagnostic performance of whole slide imaging for histopathological diagnosis was sub optimal.

Key words: Whole slide imaging, conventional microscopy, concordance rate

RESUME

CONTEXTE: La microscopie lame entière a été utilisée plus particulièrement dans le domaine de l'éducation, de la recherche et dans les consultations pour un deuxième avis. De nombreuses études ont été menées pour évaluer son utilisation en tant qu'outil de diagnostic primaire en pathologie. L'utilisation de la microscopie à lames entières pour le tissu mammaire peut être bénéfique, en particulier dans les situations où il y a une pénurie de pathologistes. Cependant, il existe peu de données sur l'utilisation de cet outil pour le diagnostique histopathologique du tissu mammaire dans des contextes où les ressources sont limitées motivant cette étude..

OBJECTIF: Déterminer la validité de la microscopie des lames entières pour le diagnostic histopathologique primaire des échantillons des tissus mammaires**.**

MÉTHODES: Il s'agit d'une étude diagnostique, descriptive cas-témoins réalisée à l'hôpital gynéco-obstétrique et pédiatrique de Yaoundé et au Centre Pasteur Cameroun. Cette étude a été réalisée sur une période de 09 mois, s'étendant du 1er octobre 2023 à juin 2024. Après avoir obtenu les autorisations éthiques et administratives, nous avons récupéré des lames de verre de tissu mammaire avec des colorations à l'hématoxyline et à l'éosine dans les archives des services de pathologie des 02 hôpitaux de l'étude. Les lames de verre ont ensuite été évaluées par un pathologiste par la microscopie conventionnel, ré-identifiées, numérisées et examinées à distance après une période de 4 semaines.

RÉSULTATS: Les taux de concordance intra-observateur entre la microscopie de la lame entière et la microscopie conventionnelle dans l'identification d'un processus pathologique et le diagnostic pathologique final étaient respectivement de 95% et 70%. Les taux de concordance inter-observateurs entre la CM et le diagnostic de référence étaient respectivement de 93,3% et 63,3% pour l'identification d'un processus pathologique et le diagnostic pathologique final. Le taux de concordance inter-observateurs entre WSI et le diagnostic de référence était de 95% et 61,7% pour l'identification des processus pathologiques et le diagnostic pathologique final, respectivement. Le degré d'accord intra-observateur de 0,49 et inter-observateurs de 0,01 et 0,02 pour CM et WSI dans l'identification d'un processus pathologique. Nous avons obtenu une sensibilité de 98,2%, une spécificité de 33,3%, une valeur prédictive positive de 96,6%, une valeur négative de 100% et l'aire sous la courbe de 0.151

CONCLUSION: Le degré d'accord intra et inter-observateur était modéré et léger. Le rendement diagnostique histopathologique était sous optimal en utilisant la microscopie de la lame entière.

Mots clés : Microscopie de la lame entière, microscopie conventionnelle, taux de concordance

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LIST OF ABBREVIATIONS AND ACRONYMS

CM	Conventional Microscopy
CPC	Centre Pasteur Cameroon
CVS	Computer Vision Syndrome
DICOM	Digital Imaging and Communications in Medicine
DP	Digital Pathology
FISH	Fluorescent In Situ Hybridization
H&E	Hematoxyline and Eosin
HGOPY	Gyneco-obstetric and Pediatric Hospital
IHC	Immunohistochemistry
IOV	Inter-observer variability
IRV	Intra-rater variability
IT	Information Technology
LIS	Laboratory Information System
PAC	Periodic Acid Shift
WSI	Whole slide imaging

CHAPTER I: INTRODUCTION

I.1 Background and Rational

The advent of the technology in medicine has brought amazing inputs to conventional medicine over the years. It has improved diagnostics, surveillance and ultimately patient care. Digital pathology (DP) is a subfield of pathology that deals with data management of digitized slides obtained from virtual microscopy. Information in digitized slides can be shared, viewed , analyzed ,and interpreted remotely [1] leading to an increases diagnostic accuracy ,lower turnaround time and better service delivery or population coverage [2]. Ample knowledge and support from leadership of the pathology laboratory and institution is of key importance for it implementation [3].

Several studies have compared Whole Slide Images and optical microscopic glass slide analysis as a diagnostic tools for primary histopathogical diagnosis. A non-inferiority study by Sanjay et al in 2018 showed is discordance rate between Whole Slide Images (4,9%) and Glass Slides (4,6%) when both slides were reevaluated within a washout period greater than 4 weeks post initial diagnosis[4]. A similar study conducted at Abdulaziz Medical City ,Saudi Arabia showed a concordance rate of 80,8% for WSI and 86,3% for GS when compared to initial diagnosis [2]. A couple of studies done in Zambia , Uganda and other African countries showed the feasibility and accuracy of using digital pathology as a primary diagnostic modality in pathology [5–7].

In Cameroon, the increased demand for pathological diagnosis particularly with the increasing burden on cancer accounts for 4% of deaths with over 20,745 cases each year [8,9].This paucity of pathologists makes it challenging for local communities to have access to their services prompting several referrals of cancer suspicious cases to urban areas which may hinder the precocious and timely diagnosis of these cases leading poorer outcomes.

A similar situation in Quebec was handled by implementing DP on a large scale so as to mitigate the non-adherence of pathologists to work in remote areas , the inability to maintain continuous services for shortage of replacements when on leave and over specialization of pathologists made it more challenging to work in small communities[10].

In Cameroon, DP has been implemented in the Adamawa region of region by a non-governmental organization to provide remote histopathological diagnosis enabling in 88.7% a pathological diagnosis when WSI scanner was used. The diagnostic accuracy of DP in our context has not been evaluated [9]. The aim of this study was to assess the possibility of using DP as a diagnostic tool

alleviate the multiple the multiple challenges faced with the precocious diagnosis of breast cancer and to provide more evidence to support the implementation of DP in our setting.

I.2 Research Question

Can whole slide images of breast tissue specimens be used to provide accurate histopathological diagnosis at HGOPY and CPC ?

I.3 Research Hypothesis

Whole slide images may be used to provide accurate histopathological diagnosis of breast tissue samples.

I.4 OBJECTIVES

I.4.1 General Objectives

To determine the validity of Whole slide imaging for primary histopathological diagnosis of breast tissue specimens at the Gyneco-obstetric and pediatric hospital of Yaounde and Centre Pasteur Cameroon.

I.4.2 Specific Objectives

1. To determine the concordance, intra-observer and inter-observer agreement of whole slide imaging and traditional microscopy for the diagnosis of breast tissue histology specimens.
2. To assess the diagnostic performance of whole slide imaging across a sample of breast tissue histology slides

CHAPTER II: LITERATURE REVIEW

II.1 Introduction and Background

Digital pathology is the conversion light microscope images on a slide into digitized files permitting pathological diagnosis to be sent remotely over long distances.

The ability to digitize an entire pathology glass slide has been transformational and engendered numerous clinical , educational and research applications [11]

‘’Digital pathology’’ emerged in the 1980s introduced by Weinstein in one of his famous editorials [12,13]. He was the first pathologist to experience telepathology as part of his multiservice between the Logan airport and the Massachusetts General hospital in 1968 using an analog technology which permitted the transmission of black and white microscopic photos[14,15].

In the 1980s the term telepathology saw its light and was used interchangeably with digital pathology. Its setup was made of a motorized microscope and a live view option of the microscopic slide. Its use was mostly limited to research and second opinion [16,17].

The 1990s was a decade of major digital breakthroughs with the advent of automated slide scanners [15,18].The first commercial slide scanner, called the BLISS (Bacus Laboratory Inc., Slide Scanner) system was designed by James Bacus in 1994 [11] . In 1999 an automated high speed system for Slide imaging and award of Whole slide imaging patent [11,19] .

Commercial WSI devices were introduced in 2001 with the Aperio (Leica) T1 being the first device produced. Each successive generation of WSI devices has been demarcated by graduated improvements in multiple functions, including scan speed, throughput, image quality, slide capacity, telepathology capabilities and z-stacking [19,20].

A major breakthrough came forth when the FDA approved the use of WSI Systems for pathology diagnostics in 2017. These systems are made up of an image acquisition subsystem(whole slide scanner) and a work station environment [19,21] .

Important improvements in the quality of the images and reduced scanning times have demonstrated that the quality of virtual images is not inferior to the microscope [15].

Clinical services were significantly altered by the COVID-19 pandemic as barrier measures such as social distancing, isolation etc, were implemented. A significant delay in cancer pathological

diagnosis and surgery for about 6 months in the United Kingdom predicted to result in about 10,760 attributable deaths.

These delays could be mitigated by the full implantation of digital pathology which will maintain the work even amidst health crises. A concept which now resonates with many pathologist who beforehand had shown reluctance to its implementation [22,23] .

II.2 Recalls

II.2.1 Anatomy and physiology of Breast

II.2.1.1 Location

Breast are paired structures located on the anterior aspect of the chest beneath the subcutaneous tissue on the ventral chest muscles and extends from the 2nd to the 6th rib having medial boundaries the sternum , lateral boundaries the mid-axillary line and the clavicles as superior boundaries. [24,25]

It is divided into four quadrants, the upper lateral (A), the upper medial (B), lower lateral (C) and the lower medial (D).

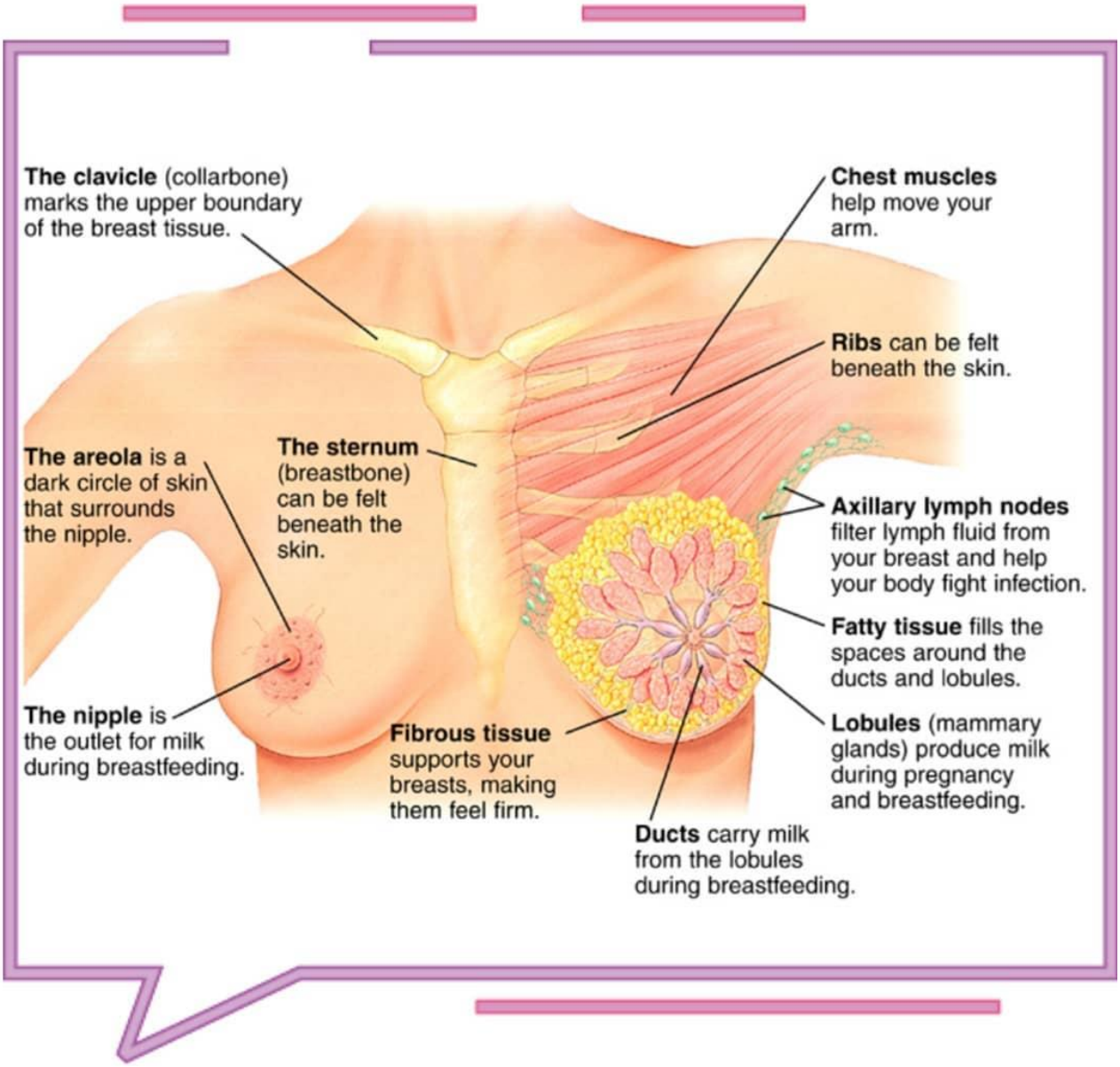

Figure 1: Boundaries of the female breast [26]

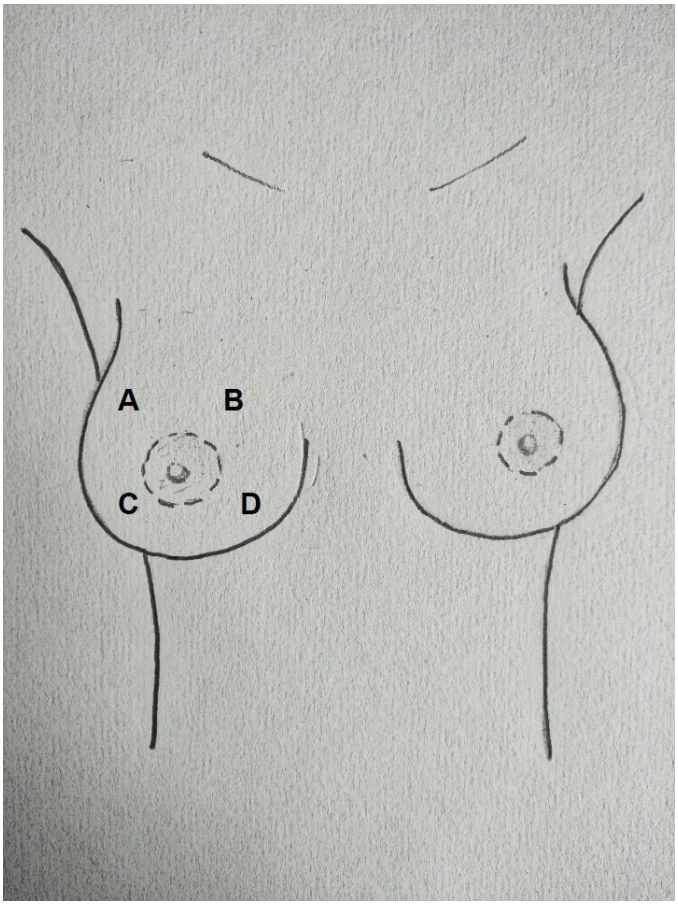

Figure 2: Quadrants of the breast [26]

II.2.1.2 Function

- Milk production
- Lactation
- Sexual arousal

II.2.1.3 Anatomical structure

Mammy gland

Breast is made up most abundantly of glandular and fatty tissue and their ratio varies among individuals.

They are modified sweat glands with a lobular organization (10-20 lobes). Its major ducts and lactiferous sinuses drain the milk to the nipples. It is under developed in men and usually non-functional.

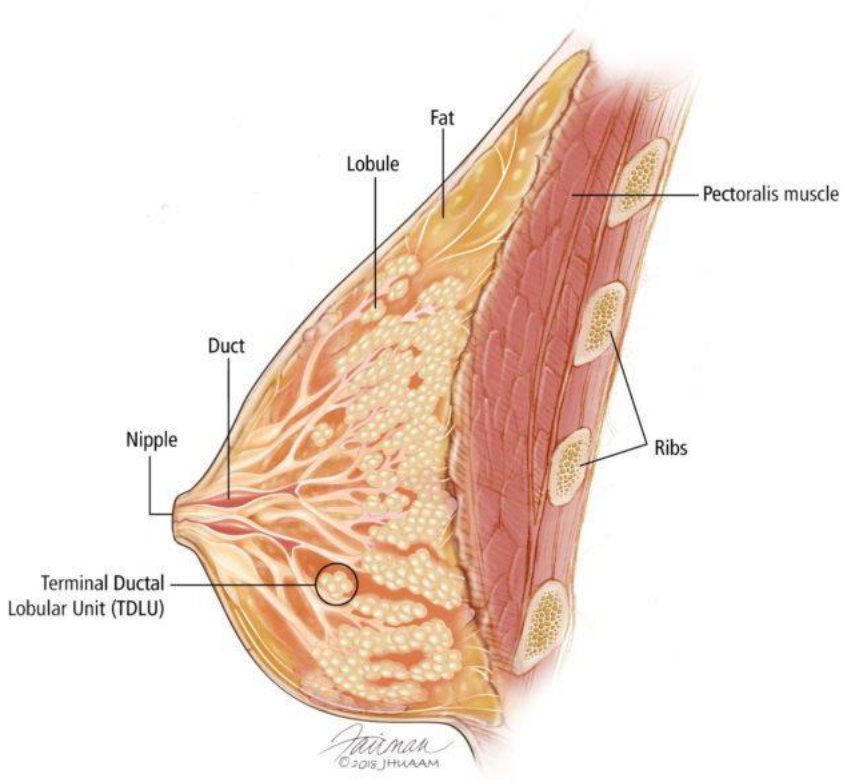

Figure 3: The internal structure of the breast [26]

Inter-lobular mammary stroma

It is the connective tissue that is found between the lobules of breast. It consists of fibrous tissue, vasculature and supporting cells that provides support to the breast and helps maintain its shape.

Mammary Papilla

They are raised projections on the breast surface. It the area in which the milk ducts and the mammary glands open unto the skin. The areolar, a dark skin pigmented disk surround the nipple.

Ligaments and fascia

They bands of connective tissues that attach the mammary glands to the skin and chest wall. It consists of the pectoral fascia and the suspensory ligament of the breast (cooper ligaments)

Vasculature

Blood is supplied to the breast via the thoracoacromial artery, internal mammary perforators (second to fifth), lateral thoracic artery, thoracodorsal artery, terminal branches of the intercostal perforators (third to eight).

Overall 60% of these blood supply is obtained from the internal mammary artery [26]

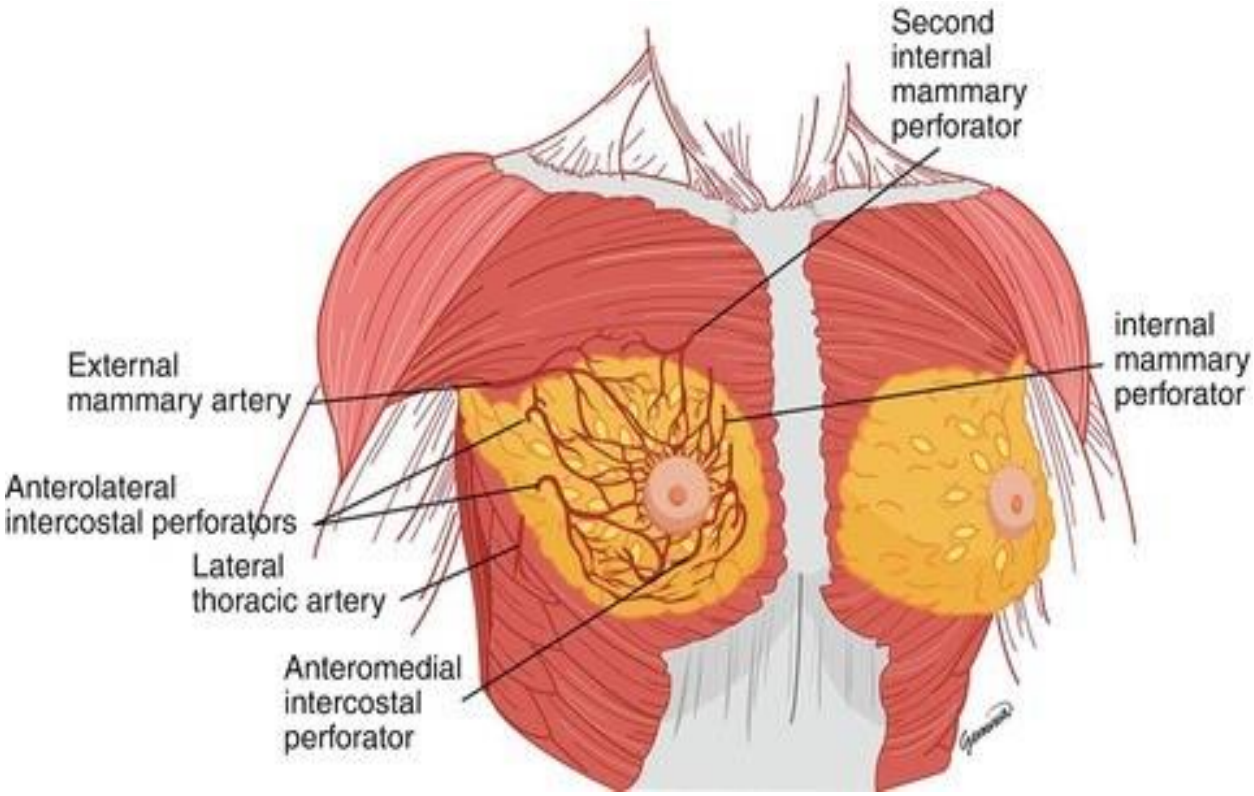

Figure 4: Arterial vascularization of breast [28]

The breast contains an extensive network of veins that can be categorized into superficial and deep veins. The superficial veins are located on the front side of the fascia and run beneath the nipple areolar complex, forming a venous plexus known as the Haller's plexus. On the other hand the deep veins are situated within the breast tissue and they connect to the veins of the chest wall, allowing for drainage of blood from the breast via the axillary and internal thoracic veins.

Lymphatics.

The lymphatic drainage system of the breast is crucial in the context of breast cancer metastasis. There are three main groups of lymph nodes that receive lymphatic fluid from the breast tissue, the axillary nodes (75%), parasternal nodes (20%) and posterior intercostal nodes (5%).

Additionally, skin of the breast has its own lymphatic drainage pathway. The lymphatic vessels from the skin drain into the axillary nodes, inferior deep cervical nodes, and infra-clavicular nodes.

Furthermore, the lymphatic drainage of the nipples and areolar region occurs through the sub-areolar lymphatic plexus. [27]

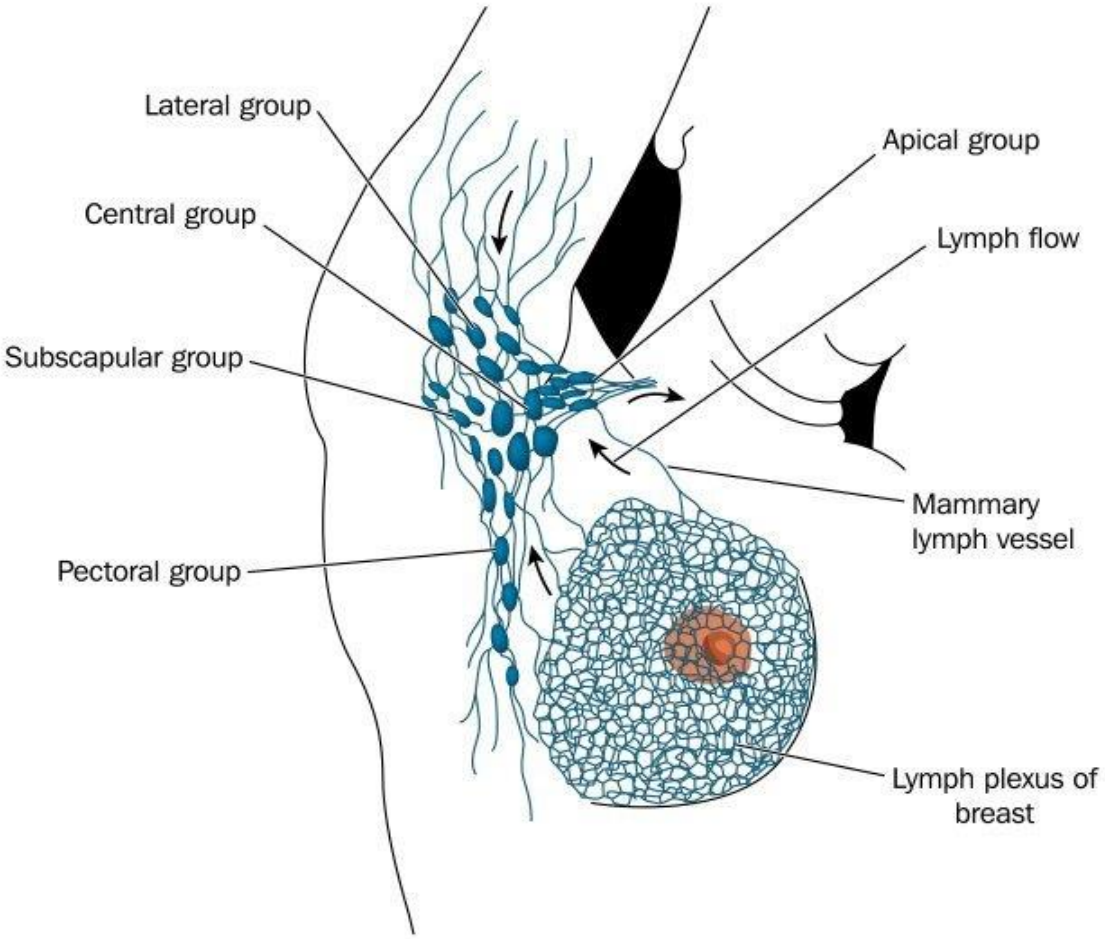

Figure 5: The five groups of axillary lymphatic nodes [30]

Innervation

The breast receives innervation from the anterior and lateral cutaneous branches of the 4^{th} to 6^{th} intercostal nerves. These nerves consist of both sensory and autonomic nerve fibers, with the autonomic fibers responsible for regulating the tone of smooth muscles and blood vessels.

II.2.2 Breast Pathology

There are a wide range of diseases that can affect the breast tissue some of which are benign and others malignant. Fibrocystic breast changes is the most common benign lesion of the breast and approximately 50% of women are likely to develop a benign breast lesion in their lifetime. [24]

Breast cancer is the most common global malignancy in women and the second most common in both sexes [8]. It accounts for 11.6% of cancer cases worldwide and studies have shown that 1 in 8 women are at risk of developing breast cancer in their course of life [8,24].

Breast pathologies are numerous amidst which we have:

- Benign breast conditions [24]
  - Fibrocystic breast changes
  - Breast cysts
  - Fibroadenoma
  - Intraductal papilloma
  - Lobular carcinoma in situ
  - Phyllodes tumor
  - Mastitis
  - Breast abscess
  - Fat necrosis
  - Mammary duct ectasia
  - Mondor disease of the breast

- Malignant breast conditions
  - Invasive ductal carcinoma
  - Invasive lobular carcinoma
  - Inflammatory breast cancer

- Non-invasive ductal carcinoma

II.2.3 Diagnostic methods for pathological breast conditions

The diagnostic modalities for pathological breast conditions are numerous and the modality of choice in first intention depends on the clinical presentation of the patient and the nature of the breast condition.

Some of these diagnostic methods are: [28,29]

- **Clinical Breast examination:** It is a non-invasive evaluation conducted to assess the breast and surrounding areas for abnormalities such as lumps, changes in skin texture, or nipple discharge. It serves as an initial assessment and can provide valuable information about the breast condition.

- **Mammography:** It is an imaging technique that utilizes low-dose X-rays to examine the breasts. It is specifically designed to detect early signs of breast cancer, even before a breast masses are present. Mammograms are frequently employed for regular breast cancer screening in asymptomatic women and can be utilized to evaluate breast abnormalities.

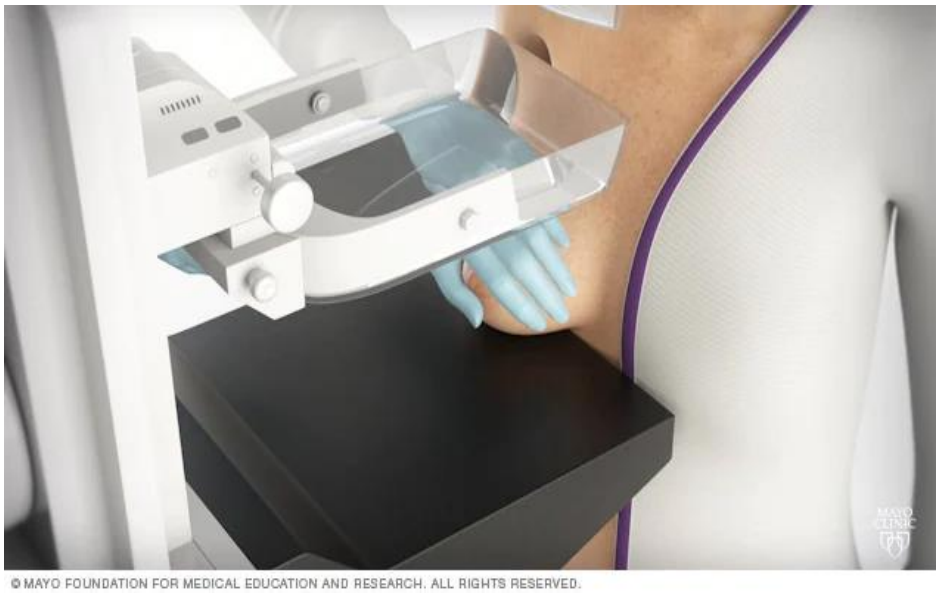

Figure 6: Mammography *[28]*

- **Breast ultrasound:** It is a diagnostic method that employs sound waves to create images of the breast tissue. It is commonly used in conjunction with mammography to further assess breast abnormalities. Ultrasound is valuable for distinguishing between fluid-filled cysts and solid masses, thus offering supplemental information regarding the characteristics of a breast lump.

- **Breast magnetic resonance imaging:** This diagnostic technique utilizes strong magnets and radio waves to generate detailed images of the breast tissue. It is typically employed as an additional tool to mammography in certain circumstances, such as evaluating women with a high risk of breast cancer or determining the extend of a known breast cancer.

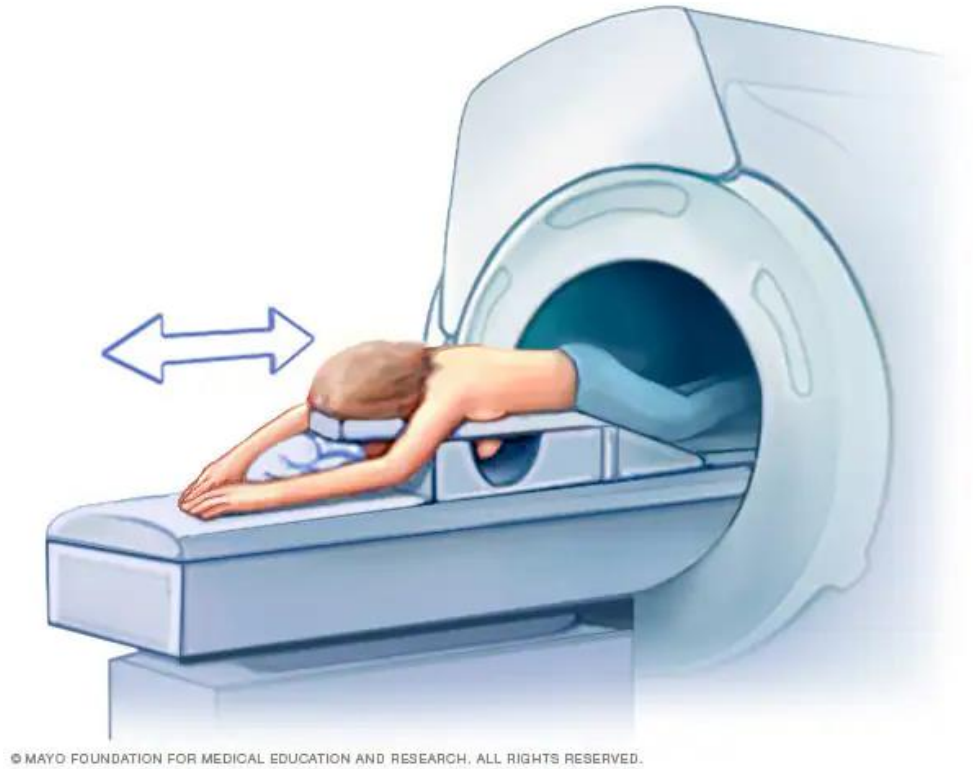

Figure 7: Magnetic resonance imaging of breast *[28]*

Biopsy: It is a diagnostic procedure that entails extracting a small tissue sample from the breast for microscopic analysis. It is considered the definitive method for diagnosing breast conditions. Various types of biopsies exists, including fine-needle aspiration biopsy, core needle biopsy, and surgical biopsies. The choice of biopsy method is determined by the specific characteristics of breast abnormality being investigated.

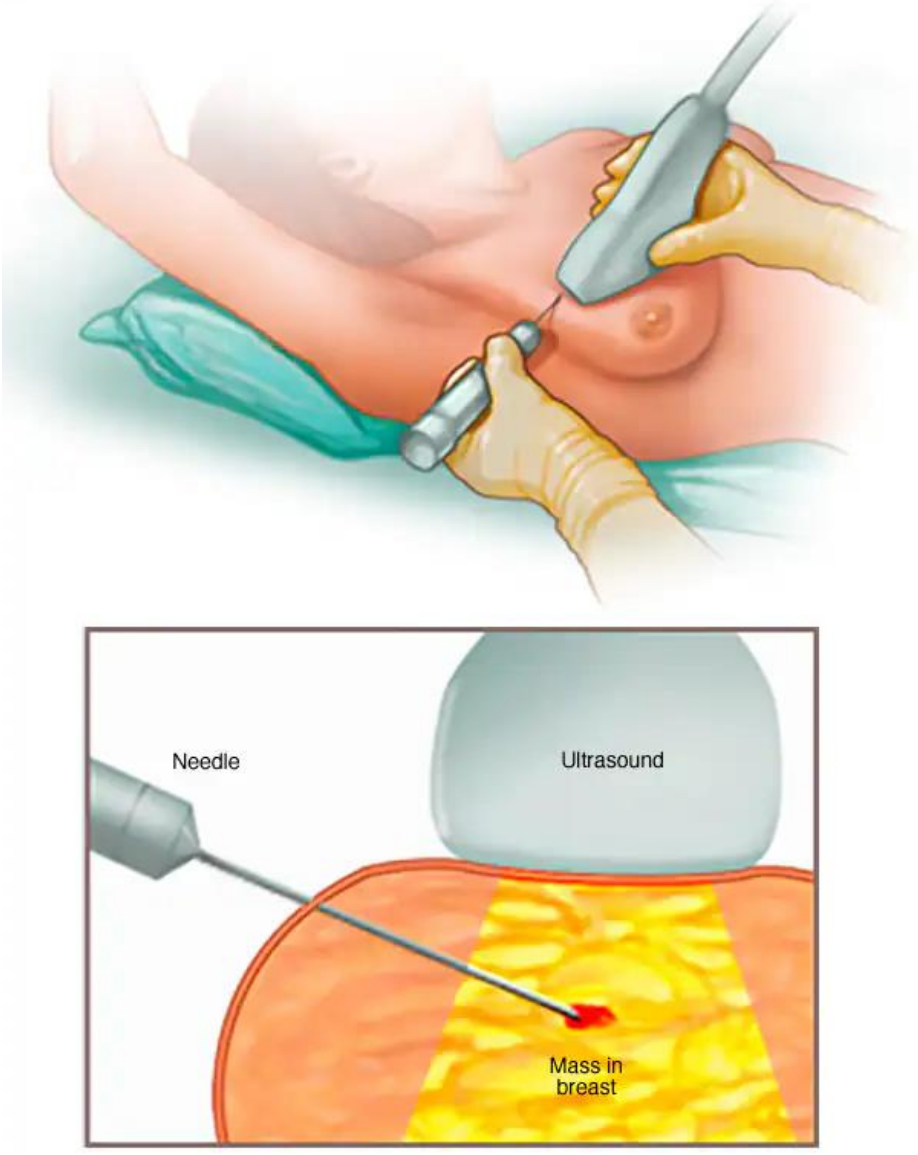

Figure 8: Core needle biopsy of breast *[28]*

II.3 Application of digital pathology

II.3.1 Technologies

- **Static and dynamic image telepathology**

Telepathology refers to the practice of pathology at a distance via the remote transmission of pathological images for interpretation and diagnostic purposes.

This technological approach has lifted boundaries linked to just a physical laboratory.

It has enhanced relationships between pathologists via remote interactions, intraoperative diagnosis as well as second opinions consults, and has improved access to pathologists in underserved areas.

Telepathology is divided in two main groups ie static telepathology, wherein still images are captured from glass slides using a microscope or slide scanned and are then transmitted to the recipient.

In dynamic telepathology these digital images are transmitted in real time via camera attached to a microscope or a digital camera [15,30] .

- **Whole slide images**

WSI is the electronic conversion of microscopic glass slides using high resolution and high speed scanners into digital images of the entire specimen that are viewed on a computer screen [31].

These images can be accessed remotely via image management software [15].

The image quality, maneuverability, interactivity and ease to share has proven their use to be more beneficial to other forms of digital images for their use education, primary diagnosis, second opinion, image analysis, and intraoperative consultation [15,30,31].

Its adoption in certain schools of Dental surgery and medicine has led to the complete desertion of microscopes [30].

Due to the different scanner types and the different software on which they run, the file format of the digital image produced is native to the scanner used.

Thereby making standardization of WSI a major challenge.

The digital imaging and communications in medicine (DICOM) which is widely used in radiology has been proposed since 2010 to resolve this impending problem but is yet to be approved [19] .

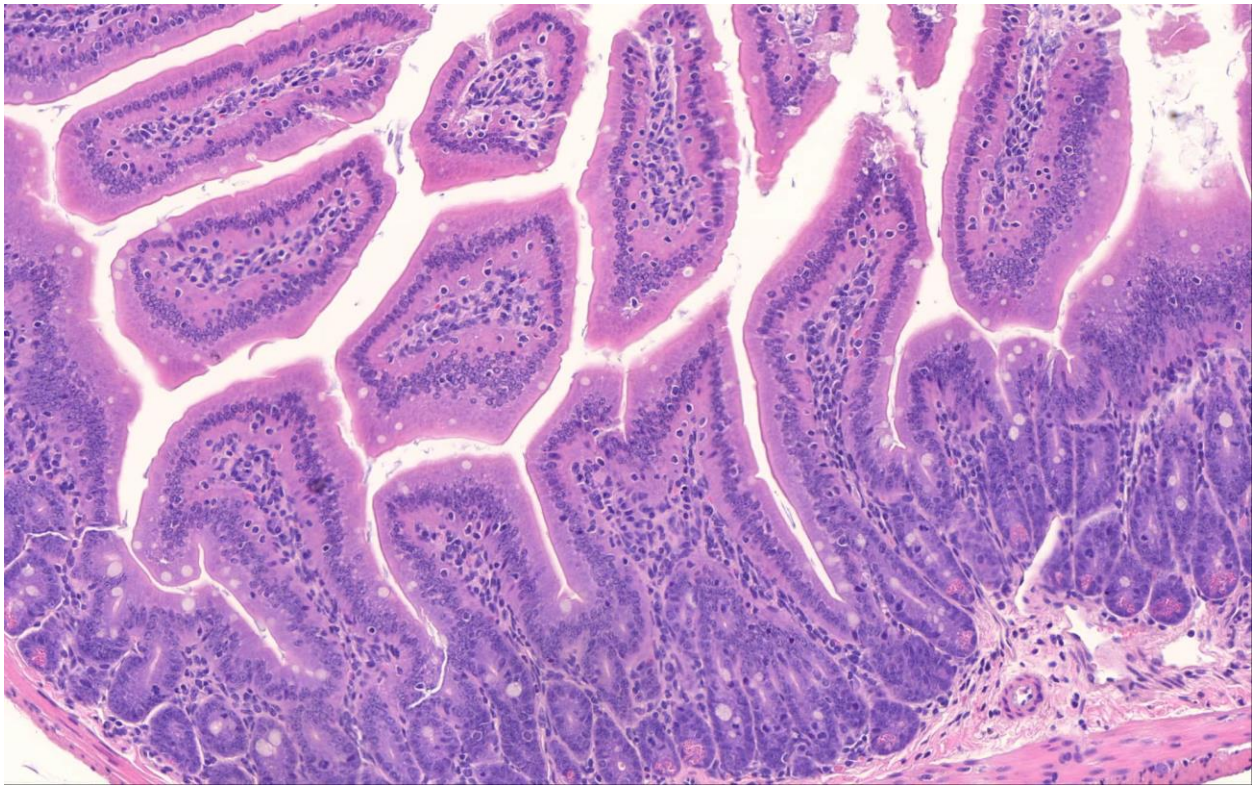

Figure 9: Whole slide image *[32]*

- **Mobile devices**

Mobile devices has certain features that provides prospects for its use in telepathology. some of which are portability and most especially affordability[31].

Smartphones with cameras equipped with image analysis algorithm and software can capture images of a glass slide [9].

These image analysis algorithms and software can permit these devices to perform complex tasks such as cell counting, identification of specific markers and morphologic analysis.

Cloud based storage capacities of these devices allow secure storage and easy access of its content which can be sent remotely to a pathologist for primary diagnosis or second opinion [30].

II.3.2 Education

Digital pathology has had a great impact in medical education and seems to be the area wherein it has been vastly used.

There is almost a complete drift from glass slide use to WSI in histology and pathology courses in medical and other health sciences.

Digitized images over microscopy based learning provides easy access to its content for it can be shared remotely , enhances collaborative learning between students and instructors via editing tools incorporated via the software viewer , permits creation of a reference library and ease of maintenance [30,31].

The afore mentioned features has grounded the use of digital pathology in medical school, pathology training , examinations , teleconferences ,E-learning , virtual workshop [15].

II.3.3 Research

Virtual storage capacities of virtual images provides an easily accessible database for research.

The diverse cellular and histology samples, population, age, gender permit epidemiological studies for the determination of patterns, risk factors and population variations.

The emergence of artificial intelligence (AI) in pathology has provided key features highly exploited by pharmaceutical companies to monitor drug capacities, monitor evolution of patients on chemotherapy, predict disease outcomes, and determine prognosis.

Digital pathology with AI via machine learning automatically analyze digital images and provide useful information for tissue classification, detection of specific cellular features, tumor grading and patient outcome.

II.4 Digital Pathology Implementation Requirement

Numerous studies have shown non-inferiority of WSI for primary cytology and histology diagnosis. Such evidence and advent of COVID-19 has lead to its implementation in many health laboratories. The material, human and financial resources warranted for its effective implementation has made it less common in resource limited countries despite the paucity of pathologists and the numerous advantages that comes with DP.

An understanding of these requirements is of primordial necessity.

These requirements include sponsorship from leadership, WSI scanners, storage, space and staffing. Each of these requirements has an essential role to play for the smooth running of digital laboratory.

- **Sponsorship from leadership**

The lack of leadership support is one of the major barriers to the implementation of DP by institutions.

Reasons for this challenge could be due to a lack of indebt understanding of the benefits of this novel diagnostic modality, an initial unclear view on return on investment, strong adherence to conventional diagnostic methods and cost for DP implementation including training of stakeholders, maintenance cost.

A clear apprehension of challenges and benefits DP by all stakeholders ie the leadership within the institution , pathologists , technical staffs of the department , and information technology (IT) team will be a pre-requisite for DP implementation.

Sponsorship could be obtained from the institution or from external sources.

- **WSI Scanners**

Since the introduction of WSI scanners since in the 1990s several types have been made available by different vendor companies [3].

These devices capture numerous images of a specimen or tissue on a microscopic glass slide at high speed and high resolution.

The different parts of the image are then stitched together to provide a full digital representation of the entire slide.

These high resolution digital images are very large about 1-4GB and require proper solutions for storage and management of such volumes of data [19,33].

With the advent of different scanner types the choice of WSI scanner types, the choice of scanner for diagnostic purposes should take into consideration the following factors (1) volume of slides (2) type of specimen(e.g tissue section slides, cytology slides, hematopathology smear) (3) feasibility of z-stack scanning (4)laboratory need for oil immersion scanning (5) types of glass slides (e.g wet, unusual size) (6) slide barcode readability (7) existing space constraints in the laboratory (8) functionality of image viewer and management system provided by vendor (9)

bidirectional integration with existing information system (10) communication protocol (e.g XML , HL7) between DP scanners and laboratory integration system(LIS) [30].

A comparative study showed significant difference between 04 anonymous whole slide scanner types on scanning different specimen types by evaluating their performance , scanning space and time per slide. A difference of about 9,6% between the most and least efficient scanner was observed when their performance was assessed [31].

The different types of whole slide scanners are grouped into 4 categories namely high throughput, low throughput, real time hybrid robotic and integrated microscopy.

These scanners have 04 components ; a light source, slide stage, objective lenses, and high resolution camera for image capture [34].

High throughput scanners

These scanners automate the process of high volume digitalization. They are able to scan over 100-1000 microscopic slides in a continuous fashion ie no interruption between loading and unloading new slides. Examples include Auron (Tissue Scope LE120), Optrascan (OS-FCL), Leica (Aperio AT2), Hamamatsu (Nanozoomeer), Philips (ultrafast) [3,19].

Figure 10: High throughput microscope slide scanner Aperio AT2 *[35]*

Low throughput scanners

These scanners are used for low to medium volume scanning ie between 2-60 slides.

They are good alternatives for laboratories who are in the initiation process of digital pathology or who need a more cost-effective scanner and or who don't have sufficient space to accommodate high throughput scanners.

They are equally solicited in situations where high throughput scanners are less efficient like in fluorescence, intraoperative, consultations or scanning with oil.

Examples include Motic (Easy scan), Hamamatsu (Nanozoomer 860), 3DHistech (Panoramic MIDI), Huron (Tissue scope LE) , Leica (Aperio LV1) [3,19].

Figure 11: Motic low throughput scanner [40]

Dynamic-robotic imaging devices

These scanner devices are used for low throughput scanning ie between 1-6 slides per slide input bay.

Pathologists can remotely have access to these devices via internet and view glass slide specimens.

It is used predominantly in telepathology for intraoperative diagnosis and consultation [3,19,36].

Integrated microscopes

They are low throughput devices, the lowest amidst afore mentioned scanners.

They are made up of a digital camera mounted on a microscope.

The emergence of specific software has ameliorated its functions from capturing still images only to capturing several images and stitching to produce a whole slide image.

The cost effectiveness of these devices makes it a good option for use in resource limited countries as an initial step into digital pathology.

Mobile devices (smartphones) when attached to microscope has equally been used to capture images from microscopic slides [9,19].

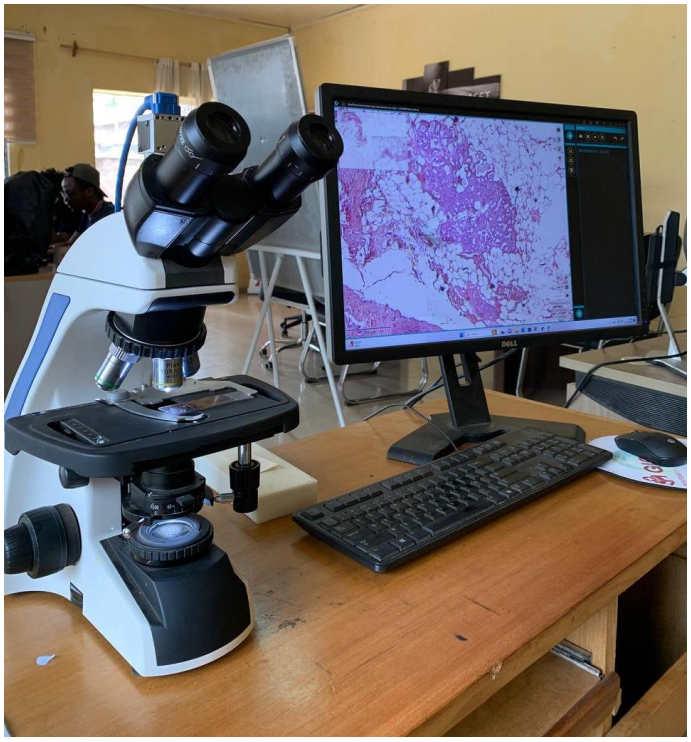

Figure 12: Intergrated microscope scanner

- **Storage**

WSI are high resolution images that require high resolution storage to prevent data compression. Compression and decompression of digital images can lead to data losses there by altering image quality and hence diagnosis.

Digitized images weigh about 1-4GB per slide scanned.

An estimate of total storage required per year can be calculated by dividing the number of stained glass slides to be scanned annually by 500 ie if 100,000 slides are to be generated annually, 200 terabyte of storage space will be needed annually.

Digital images could be saved on-premises,in the cloud, network-atttached storage, commercial databases. Running such centralized systems are financially demanding and exposes to certain risks such as security attacks , security breaches , and violation of patient privacy as cloud provider or database network administrator controls security and the database [3,37].

- **Space**

To provide a good work flow, specific dimensions and locations should be attributed to the hardware components of a DP system in a laboratory.

The lean system of organization seems to be widely used in DP laboratories. These space allocations could be divided into a pre-scanner workstation (storage room, histology area, cytology area, processing area, immunohistochemistry area, histochemistry area etc), scanner work station that should ideally be in non-traffic areas (scanning device), post-scanner segment (pathologist work station, archive room) [38].

The proper allocation of these designated areas will increase efficiency, reduce turnaround time, and improve satisfaction of the personnel in-charge of digitizing the slides.

- **Staffing**

Implementation of a new diagnostic modality will necessitate repositioning of the pathology department personnel and may require hiring more staffs to meet up the work burden on new aspects of the work chain such as network and IT specialists needed for operational needs, software development and maintenance.

Team work between pathologists, data scientist, engineers, and technicians will be crucial for proper workflow [3].

Additional training of pathologists and technicians for apprehension of new modifications to the laboratory such as space, equipment, IT infrastructure, quality control and workflow [38].

These demands and change on the departments daily routine might be a reason for reluctance to digital pathology implementation.

II.5 Digital pathology work flow [39]

Digital work flow refers to the series of interconnected steps or processes that are carried out using digital tools generally in a computerized environment.

In digital pathology these steps involves accessioning, grossing, processing embedding, sectioning, staining and scanning, assembling, delivering, archiving.

- Accessioning of case is done automatically by registering in the laboratory information system and attributing a case number.

  These reduces risk of transcription errors as compared to analog accessioning.

  It permits the registration and tracking of specimens via the assigning of a unique identifier such as patient ID, specimen container ID, sample IDs , block ID , and slide ID
- Grossing refers to the digitization and virtualization the examination process. The identification code is scanned to have access to the patient file to prevent transcription errors. Using a camera a high resolution image of the specimen is taken to create a digital representation of the macroscopic features as it is in container. These photographs are then introduces into the patient patient/case file at the LIS to prevent mismatches and time loss. The sample is macroscopically described, dictated and converted to text via voice recognition function of the LIS. Cassettes are then printed with the identification code of the sample to be tracked in subsequent work stations.
- Processing and embedding; In preparation for embedding the specimens are dehydrated , cleared and infiltrated with a suitable embedding medium mostly paraffin to form paraffin blocks. The barcode on cassettes are scanned and the image is compared with that obtained at the grossing phase to exclude the loss of biological content. Embedding ensures the production of good quality digital images.

- Sectioning; The tissue blocks are cut into thin sections using a microtome. The paraffin block may be photographed to assess for loss of material.
- At the staining work station the slides are scanned via the barcode to determine the type of staining technique to be applied as initially recorded in the LIS. Staining can be done via Hematoxylin and Eosin (H&E) which is widely used for histopathological analysis or via special stains such as Periodic Acid-Schiff (PAC), Immunohistochemistry (IHC), or Fluorescent In Situ Hybridization CFISH). These stains enhances the visibility and contrast of tissues or cells on a slide.
- The mounter, coverslip type, mounting medium are carefully selected for the scanner to be calibrated. The stained glass slides is loaded on the scanning platform. The scanning software is configured to determine the resolution, magnification, and focus level. Scanning begins by systematically moving the stage with the slides while capturing images of the slide at multiple views. The captured images are then stitched together to produce a single digital image of the entire glass slide. This is followed by a quality control processes and the slides are archived automatically by aide of the barcode.

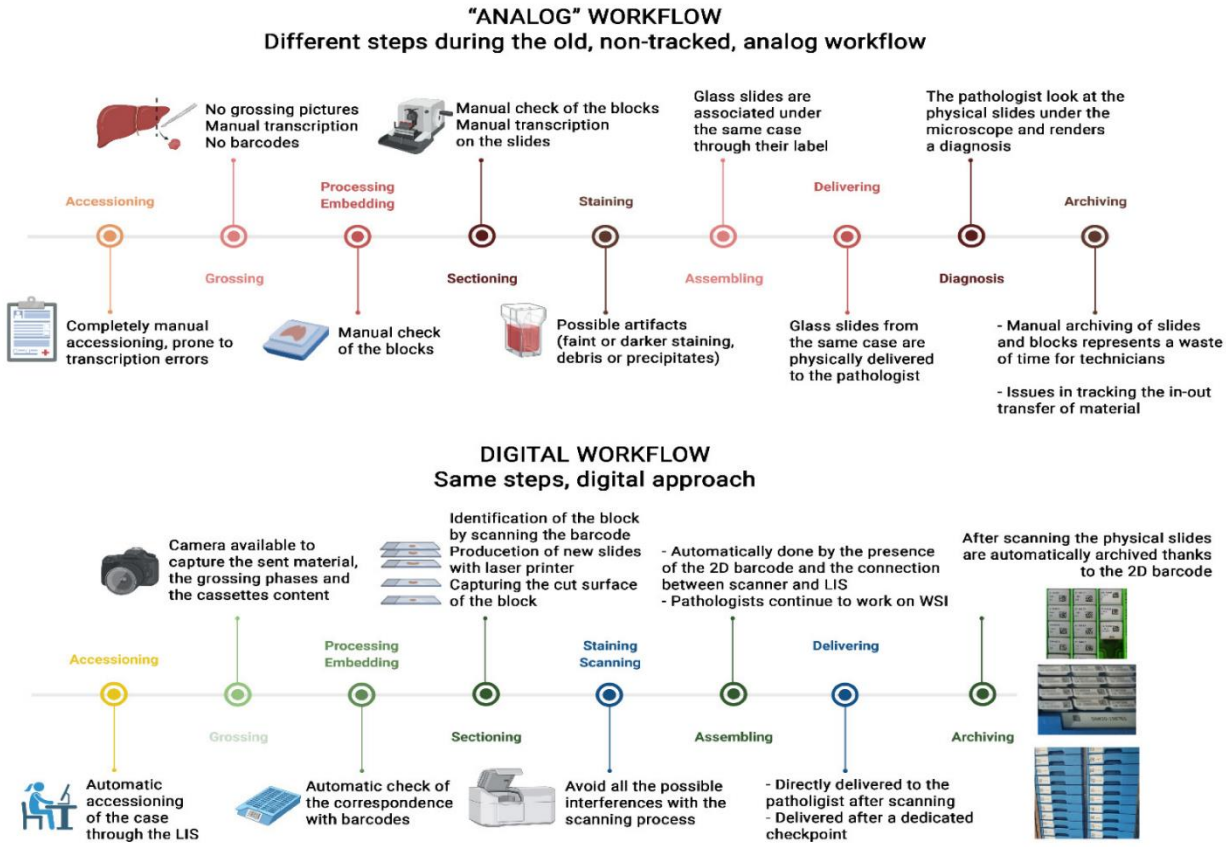

Figure 13: Comparison of traditional microscopy and digital pathology workflow [44]

II.6 Advantages and disadvantages of digital pathology

The efficiency and accuracy of digital pathology for primary diagnosis has been proven in literature, nevertheless its full implantation is hindered by certain known demands and short comings that come with such a system. Some of which are,

- The cost of implementation of a digital laboratory is quiet challenging most especially in resource limited countries. Scanners devices, monitors and display screens, high performance computers, storage systems, IT infrastructure, software needed makes it very costly.
- Nevertheless certain studies have shown a return on investment and profit making when projecting its use over a 5 year duration [16]
- Stitch artifacts which are produced when adjacent images are superimposed requires rescans which is time consuming. Z-stacking which scans slides in multiple planes

provides a solution to this problem but its use has been limited to research as the image produced are 5 folds more heavier.

- Difficulty in detecting microorganisms, mitosis and dysplasia for higher scanner resolution is needed.
- Small particles are left out during the pre-scanning process for it is done at low resolution before the pre-scanned image is then properly magnified. Review the pre-scanned and final Image by pathologists for loss of material will mostly resolve this problem.
- Occupational health problems such as computer vision syndrome (CVS) and musculoskeletal injuries are impending issues that haven't much been addressed. A study showed an increased incidence of CVS in individuals with screen time more than 4 hours daily [16]. Regular breaks, proper-lighting, anti-glare filters will improve visual comport and mitigate occurrence of CVS.

Table I. *Advantages and disadvantages of digital pathology*

Digital pathology feature	Advantages	Disadvantages
In-house telepathology	Quick second opinion Social distancing	Second opinion overuse (interrupted work-flow) Decreased interpersonal (face to face) communication
Extramural telepathology	Service for remote/understaffed areas Specialization through DP in low volume labs Home-office use Healthcare cost reduction through global histopathology market	Social isolation in remote telepathology Loss of remote on-site expertise through home office. Wage competition through global histology market

Consultation telepathology	Quick access possible No physical slide transfer Lower threshold for consultation due to shorter turnaround time	No tissue block available for additional stains/molecular essays. Consulted pathologists unaccustomed to work-up (stain/scanner calibration) at primary center. Compatibility issues due to diverse proprietary DP formats Possible medico-legal implications due to restricted work-up
WSI-general	No physical slide distribution No fading of stored slides No irretrievable/lost slides Shorter sign-out time Reduced misidentification of slides due to barcoded slides automatically allocated to the case Easy dynamic workload allocation (e.g management of backlogged work,redistribution in case of sick leave	Time to evaluable-ready slide increased due to additional scan time Integration into a laboratory information system for full efficiency gains needed Regular calibration required (scanner/display) Small particles omitted by scan Artifacts (out of focus area and digital stitching artifacts Increased IT-dependence compared to optical microscopy
WSI reporting/viewer experience	Parallel (side-by-side) viewing ,digital slide superposition Shorter sign-out time Quick access to prior slides. Less immunochemistry Facilitates slide presentation at multidisciplinary tumor board	Slower evaluation compared to optical microscope Mostly only single focus plane in routine causing difficulty in interpretation Some structures harder to recognize WSI

	Easy image sharing in clinical communications Computational pathology possible Occupational health: less neck strain, more flexible posture	Polarization not possible on DP Extra training for safe practice required if not DP career start Easy availability of prior digital slides might shift medico-legal onus towards more extensive re-examination Dual infrastructure generally necessary (glass and digital) Computer vision syndrome
WSI-image analysis, ML/AI	Faster/efficient and more accurate measurements/quantification Exact quantification of tumor cell content for molecular analyses Digital enhancement of image features AI for second-read safety net Direct link morphology to clinical parameters “novel biomarker” beyond human recognition Inspection/correction of suggestions from AI-apps in development on WSI-viewer. “human-in-loop interaction”	Benefits of more accurate quantification not necessarily clinically relevant Applications beyond human evaluation not yet approved/used for clinical management AI intranparent (“black blox”) Regulatory oversight challenges with self-modifying (adaptive) AI as algorithm/performance notconstant over time

WSI-teaching	Digital images for presentation and exams readily available Remote teaching and self-study Increased student motivation, modern appeal.	None
Cost and efficiency gains	Work time saved through faster turnaround times Decreased auxiliary technique(less immunochemistry) Decreased physical slide-transfer cost.	DP implementation and maintenance and storage cost add to current fixed cost if productive gains remain unrealized Dual infrastructure cost Glass and digital storage still generally deemed necessary Technical expert knowledge for hardware acquisition needed

II.7 CONCLUSION

Digital pathology has gained grounds in many domains out of just the pathological diagnosis due to the ease with which its data can be obtained in time, managed and transferred. Its implementation requires financial, human resources and a good apprehension of the workflow. DP has several advantages but like every system has its pitfalls. The paucity of pathologists in resource limited countries makes digital pathology a good alternative for histopathological diagnosis, not necessarily as a total replacement to conventional microscopy but as an added diagnostic modality.

II.8 REVIEW OF PREVIOUS STUDIES

II.8.1 In the World

- **Validation of whole slide imaging for frozen section diagnosis of lymph node metastasis: A retrospective study in Thailand, Kantasiripitak et al, 2022.**

295 frozen section (FS) slides were included in this study with objective to assess lymph node metastasis.03 observers with different pathologic experiences participated in the study.

The FS slides were digitized using a virtual microscope scanner with x40 optical magnification.

Each participating pathologist reviewed the FS slides via CM and virtual microscopy within a washout period of 2 weeks.

The intra-observer and inter-observer agreement of WSI and GS diagnoses were high with a kappa value of >0,84 (almost perfect agreement) showing that WSI provides accurate FS diagnoses of lymph node metastasis.

- **Whole slide imaging versus microscopy for primary diagnosis in surgical pathology—A multicenter blinded randomized non-inferiority of 1992 cases study in USA Sanjay et al, 2018**

This study was conducted by Sanjay et al in 4 institutions in the United States of America within a 14 months period to compare microscopy with WSI for primary diagnosis in surgical pathology 1192 of surgical pathology cases (biopsies and resections, including H&E, IHC and special stains) from 20 organ systems were reviewed by sixteen pathologists.

Cases were interpreted by microscopy or WSI, followed by a wash-out period of greater than or equal to 4 weeks. After the washout period same pathologist re-interpreted the case using the alternative diagnostic modality and both diagnosis were compared to the reference standard diagnosis.

(1)The major discordance rate with the reference standard diagnosis was 4.9% for WSI and 4.6% for microscopy. (2) The difference between major discordance rate was 0.4% (95% confidence interval). (3)Gynecological pathology had the least discordance rate of 1.2% for WSI and microscopy and the highest discordance was observed in endocrine pathology.

This study showed that WSI is non-inferior to microscopy for primary diagnosis in surgical pathology

- **Validation of diagnostic accuracy using digital slides in routine histopathology—A retrospective comparative study in Hungary Fonyad et al, 2012**

A retrospective study was conducted by Fonyad et al to evaluate diagnostic accuracy of digital slides in routine histopathology. 306 cases from 9 organ systems (surgical resections and biopsies) were selected from the archives from 1998 to 2007 and were digitized using a slide scanner at x20 magnification.

8 pathologists who were specialists in subfields of pathology and familiar with digital pathology participated in the study. One was a junior consultant while the 7 others had a mean working experience of 21 years in pathology. Observers were assigned cases in both the subspecialty and general cases.

The observers rendered diagnosis using digital microscopy and optical microscopy. Diagnosis were in full agreement by 88.2 and out of incoherent cases (36) only 2.3% (7 cases) were graded relevant by a consensus of pathologists.

When non-field specific cases were excluded, there was about 30% incoherent diagnosis. Results of the most experienced pathologist was faultless when non-field cases were excluded.

These findings suggested that,

(1)Digital microscopy based histopathology diagnosis is coherent with that of optical microscopy.

(2)The competence of pathologists is an important factor in digital microscopy diagnosis.

- **Intra-observer reproducibility of whole slide imaging for the primary diagnosis of breast needle biopsies in USA, Reyes et al, 2014**

Similarly, Reyes et al conducted a study to assess the reproducibility of CM and WSI. 103 core needle breast biopsy cases were selected for this study. The microscopic slides were digitized using a slide scanner with x20 magnification. These cases were reviewed by 03 pathologist. Firstly via CM and 2 to 3 weeks later via CM again to establish a baseline diagnosis. After a washout period of 2-3 weeks a review of the WSI were done. The degree of disagreement between CM versus CM, CM versus WSI was determined.

The intra-observer variability for CM versus CM was 4%, 7%, 0% for observers 1,2 and 3 respectively and a variability of 1%, 4%, 1% for CM versus WSI for the same observer.

The diagnostic disagreement were between ductal hyperplasia and atypical ductal hyperplasia.

There were no diagnostic disagreement between benign versus malignant cases.

II.8.2. In Africa

- **Feasibility and diagnostic accuracy of internet-based dynamic telepathology between Uganda and Germany. A retrospective study in Uganda, Wamala et al, 2011.**

At the Mulango hospital in Uganda, 96 cases were examined 96 by pathologists via telemicroscopy through the internet in Fuerth Hospital in Germany.

The pathologist at the remote site was able to control the focus, choose field and adjust brightness and magnification. About 30 minutes required by the pathologist to understand the functioning of the telepathology system and 4-25 minutes to read the case and provide the diagnosis.

The diagnosis obtained remotely was then compared to onsite optical microscopic diagnosis made by a consensus of pathologists.

A 97% concordance in the diagnosis was obtained. Disease morphologically challenging to diagnose such as soft tissue sarcoma and primitive tumors were incriminated as potential causes for the 3% discordance. Showing the feasibility and accuracy of such a system for diagnostic purposes.

- **Virtual surgical pathology in underdeveloped countries. Study in Zambia, Pagni et al, 2011**

Similarly, a prospective study was carried out by Pagni and associates in Zambia in the Mtendere missions' hospital in collaboration with Patologi Oltre Frontiera association based in Italy as from April 1 to October 31 2007. The goal of the study was to evaluate the accuracy of surgical virtual pathology in a resource limited milieu.

322 cases(261 surgical and 61 extracervical) were stained using standard procedures on site and scanned using Aperio Scanner Scan Scope CS at x20 and x40 for histology and cytology slides respectively.

The specimens were evaluated via optical microscopy on site and via telemedicine.

The diagnosis obtained from both modalities was compared and assessed. The cytology cases revealed a 100% concordance in the diagnosis and an 87.7% concordance was obtained for the

surgical specimens. Special staining techniques unavailable on site was reported to one of the factors that contributed to the 12.3% discordance rate.

II.8.3 In Cameroon

- **Digital pathology in Cameroon. A retrospective study, Gruber-Mosenbacher et al, 2021.**

In the Adamawa region of Cameroon at the Ngaoubela District hospital a comparative study was done to assess diagnostic certainty of using digital images obtained from an Iphone camera attached to the eyepiece of a microscope between 2018 to July 2019 and a portable WSI scanner between July 2019 to December 2020.

101 camera image cases and 273 WSI were obtained. According to their report, the rate of non-diagnostic images was reduced from 16.8% to 5.5% with the application of WSI despite using only hematoxylin and Eosin staining technique.

Conclusion

With the all the evidence that has been made known in literature, it clear without no iota of doubts that a digital pathology system provides accurate histopathology and cytopathology diagnosis and its use as an alternative and complementary diagnostic modality in our context with very few pathologists will be beneficial to underserved communities. It is for this reason that we saw it necessary to dwell on this.

CHAPTER III: METHODOLOGY

III.1 TYPE OF STUDY.

- Diagnostic study

III.2 SITE OF STUDY.

This study was carried out at the Pathology department of the Gyneco-obstetric and pediatric hospital of Yaounde (HGOPY) and at Centre Pasteur Cameroon. HGOPY is a teaching hospital created on the 28th of March 2002. It has several units principally Gynecological, Pediatric, Neonatology, Surgical and Pathology. Our point of interest was the pathology unit which receives several referrals from other health structures in Yaounde and other remote communities.

Centre Pasteur of Cameroon was created in 1959 is a public administrative institution of the ministry of public health with financial autonomy. It has 4 departments, a scientific department which carries out research, public health and food/water quality control, a medical department in-charge of routine medical biology, vaccination and training activities, an administrative and financial department and the delegation department.

III.3 PERIOD OF STUDY

This study was carried out for a period of 09 months, extending from October 1st 2023 to June 2024. Data management and writing of full thesis followed from 22 April 2024 to June 2024.

III.4 STUDY POPULATION

- Practicing pathologists at the Yaoundé Gyneco-obstetric hospital and Centre Pasteur of Cameroon with different degrees of expertise in pathology.
- Breast tissue biopsy slide with hematoxylin and eosin stain

III.4.1 Inclusion criteria

- **For glass slides**
    - Breast tissue biopsy slides of good quality with complete clinical information.
    - Breast tissue biopsy slides with a single case
- **For participants**
    - Practicing pathologists with over 15 years of working experience and pathologists with less than 5 years of working experience.

III.4.2 Exclusion criteria

- Cases with multiple slides
- Over represented cases

III.4.3 Sample Size

Sampling was non-probabilistic and based on the 2021 recommendations of the College of American pathologist on the validation of whole slide imaging systems for diagnostic purposes in pathology, a sample size of 60 microscopic glass slides was chosen for this study [40]

III.5 Administrative Formalities

The research protocol was written and submitted to supervisors and thereafter we applied for research authorization and ethical clearance from HGOPY, Centre Pasteur Cameroon, as well as Institutions Review Board of the Faculty of Medicine and Biomedical Sciences (FMBS) Yaounde 1.

III.6 Procedure

Microscopic glass slides from the pathology department of HGOPY and Centre Pasteur Cameroon were retrieved from the archives and quality control was done by a pathologist. Only breast biopsy cases with a single slide and H&E stain were selected.

These glass slides were then de-identified and attributed new codes. The two participating pathologists then reviewed the glass slides using conventional microscopy.

The microscopic diagnosis of the most experienced pathologist was considered as the Gold standard diagnosis.

These glass slides were then Scanned at x10 and x20 magnification using a locally build integrated microscope scanner and compatible software.

The whole slide images were attributed new codes, randomized and remotely sent to a digital platform from whence the digital review was done 4 weeks later by the reading pathologist of the study.

The diagnosis obtained via glass microscopy and whole slide imaging by the reading pathologist was compared and the degree of agreement was assessed.

The diagnostic review via conventional microscopy and whole slide imaging was then compared to the reference diagnosis and the degree of agreements were assessed.

The measures of diagnostic accuracy for whole slide imaging for the reading pathologist was the evaluated.

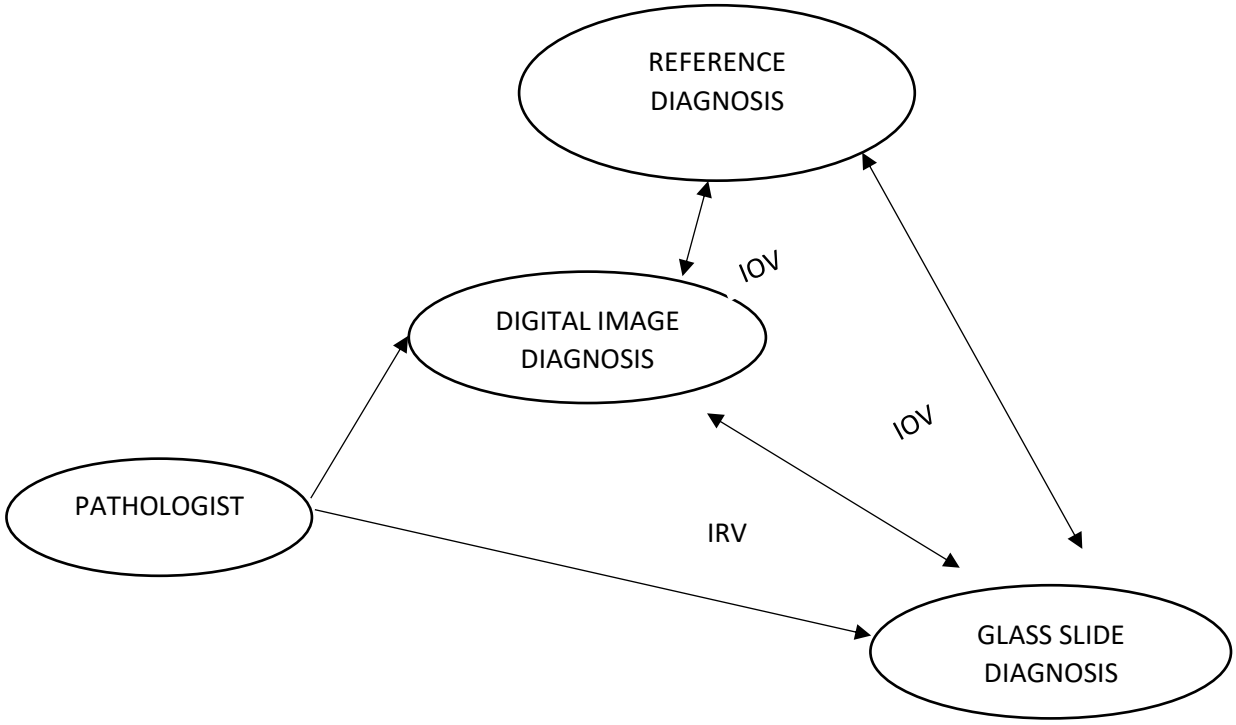

Figure 14: *Flowchart of WSI and glass slide review.*

III.7 Study resources

III.7.1. Data collection and management

- Pre-established data collection sheet
- Microscopic glass slides
- Personal computer
- Intergrated microscope
- Writing materials (paper, pen, pencil)
- Microsoft package
- USB drive
- WIFI

III.7.2 Human Resources

❖ **Main investigator**

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- Statistician

III.8 Data Analysis

Data was entered and analyzed using the statistical software EPI Info version 7.2.5.0. Cohen's kappa was analyzed using SPSS version 27 using a confidence interval of 95%. The major descriptive analysis involved were calculations of frequency and percentages. The results were presented in figures and tables.

III.9 Ethical consideration

Ethical considerations were followed in accordance with the Helsinki Declaration which goes as thus "it is the duty of physicians who are involved in medical research to protect the life, health, dignity, intergrity, right, to sefl-determination, privacy, and confidentiality of personal information of research subjects"

Before embarking on data collection, we requested and obtained ethical clearance from the ethical committee of the Faculty of Medicine and Biomedical Sciences, University of Yaounde 1.

We equally requested administrative authorization from the director of HGOPY and Centre Pasteur Cameroon to carry out the study.

CHAPTER IV: RESULTS

IV.1 CASE SELECTION

For this study we collected breast tissue biopsy cases from the archives of pathology department of HGOPY and CPC from September 4th 2023 to January 26st 2024. The total number of represented cases were 92. 22 cases which had multiple slides were excluded and a total number of 60 slides were retained for the study.

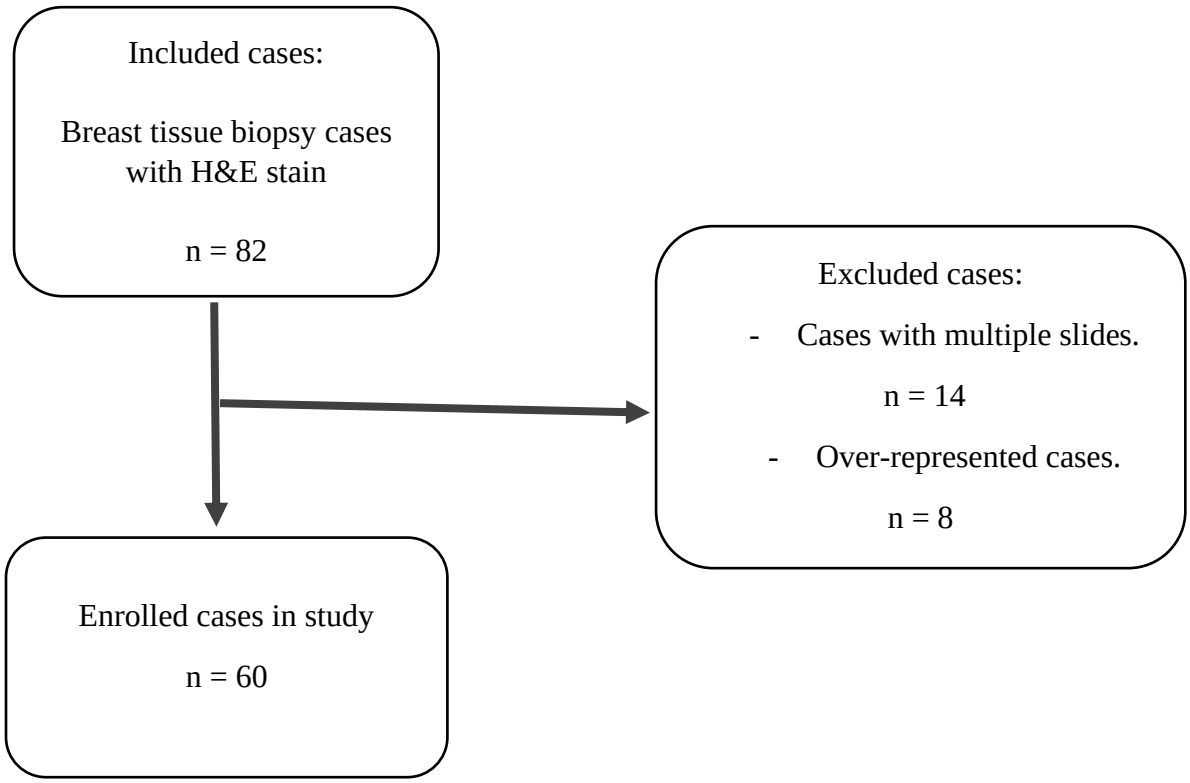

Figure 15: *Case selection flowchart.*

IV.2 DIAGNOSTIC RESULTS

IV.2.1 Microscopic Gold standard diagnostic results by most experienced pathologist.

Among the 60 breast tissue biopsies were 59 pathologic cases and 01 non-pathologic case. These cases were precisely, 29 invasive ductal carcinomas, 10 fibroscystic breast changes, 05 fibro-adenoma, 05 ductal hyperplasia, 03 mastitis, 03 invasive lobular carcinoma, 02 fat necrosis, 01 phylloides, 01 non-pathologic and 01 intraductal papilloma case as shown in Table II.

Table II. *Gold standard microscopic diagnosis of 60 breast tissue biopsies included in the study.*

Variable	n	%
General diagnosis		
Pathologic	59	98.3
Non-pathologic	01	1.7
Specific diagnosis		
Invasive ductal carcinoma	29	48.3
Fibrocystic breast changes	10	16.6
Fibro-adenoma	05	8.3
Ductal hyperplasia	05	8.3
Mastitis	03	5
Invasive lobular carcinoma	03	5
Fat necrosis	02	3.3
Phyllodes	01	1.7
Intraductal papilloma	01	1.7
Non-pathologic	01	1.7

IV.2.2 Diagnostic results for reading pathologist

Using conventional microscopy, 58 cases were observed to be pathologic and 02 cases were non-pathologic. Amidst these cases, there were 27 invasive ductal carcinoma, 07 ductal hyperplasia, 06 fibrocystic breast changes, 05 mastitis, 05 invasive lobular carcinoma, 04 sclerosing adenosis, 03 fibro-adenoma, 01 sarcoma as seen in Table III

Using whole slide imaging, 58 cases were observed to be pathologic and 02 cases were non-pathologic. Among them were, 34 invasive ductal carcinoma, 02 ductal hyperplasia, 03 fibrocystic breast changes, 04 mastitis, 05 invasive lobular carcinoma, 03 sclerosing adenosis, 03 fibro-adenoma, 03 intraductal papilloma, 01 sarcoma and 02 non-pathologic cases as seen in Table III

Table III. *Diagnosis of reading pathologist of the 60 breast tissue biopsies via conventional microscopy and whole slide imaging.*

	CM		WSI	
Variable	**n**	**%**	**n**	**%**
General diagnosis				
Pathologic	58	96.7	58	96.7
Non-pathologic	02	3.3	02	3.3
Specific diagnosis				
Invasive ductal carcinoma	27	45	34	56.7
Ductal hyperplasia	07	11.7	02	3.3
Fibrocystic breast changes	06	10	03	5
Mastitis	05	8.3	04	6.7
Invasive lobular carcinoma	05	8.3	05	8.3
Sclerosing adenosis	04	6.7	03	5
Fibro-adenoma	03	5	03	5
Intraductal papilloma	-	-	03	5
Sarcoma	01	1.7	01	1.7
Non-pathologic	02	3.3	02	3.3

CM: conventional microscopy, WSI: whole slide imaging.

IV.3 CONCORDANCE

IV.3.1 Agreement rate and degree of agreement

IV.3.1.1 Agreement rate and degree of agreement for identification of a pathologic process.

Table IV shows the 57 accord cases and 03 disaccord when the diagnosis via whole slide imaging were compared to the diagnosis via glass microscopy in the identification of a pathologic process giving a concordance rate of **95%.**

Table IV. *Intra-observer concordance rate between whole slide imaging and conventional microscopy in the identification of a pathologic process.*

Variable	**n**	**%**
Concordant	57	95
Discordant	03	05

WSI: whole slide imaging, CM: conventional microscopy

Table V shows the accord in 56 cases and disaccord in 04 cases when the diagnosis via conventional microscopy were compared to the reference diagnosis in the identification of a pathologic process giving a concordance rate of **93.3%.**

Table V. *Inter-observer concordance rate between conventional microscopy diagnosis and gold standard microscopic diagnosis in the identification of a pathologic process.*

Variable	**n**	**%**
Concordant	56	93.3
Discordant	04	6.7

CM: conventional microscopy

Table VI shows the accord in 57 cases and disaccord in 03 cases when the diagnosis via whole slide imaging were compared to the reference diagnosis in the identification of a pathologic process giving a concordance rate of 95**%.**

Table VI. *Inter-observer concordance rate between whole slide imaging diagnosis and the gold standard microscopic diagnosis in the identification of a pathologic process.*

Variable	**n**	**%**
Concordant	57	95
Discordant	03	05

WSI: whole slide imaging

Table VII shows a Cohen's kappa score of **0.49** demonstrating moderate agreement between WSI and CM obtained when the diagnosis of conventional microscopy was compared to the diagnosis obtained via whole slide imaging in the investigation of a pathologic process. 57 cases were correctly identified by both modalities (TP), no case was falsely identified as non-pathology via whole imaging (FN), 01 case was correctly identified as non-pathologic (TN) and 02 cases were incorrectly identified as pathologic (FP).

Table VII. *Intra-observer agreement between whole slide imaging and conventional microscopy in the identification of a pathologic process.*

CM WSI	Pathologic	Non-pathologic
Pathologic	57	2
Non-pathologic	0	1

WSI: whole slide imaging, CM: conventional microscopy, K = 0.49

Table VIII shows a Cohen's kappa score of **0.02** demonstrating slight agreement when the diagnosis by conventional microscopy was compared to the reference diagnosis in the investigation of a pathologic process. 56 cases were correctly identified by both modalities (TP), 03 cases were falsely identified as non-pathology via conventional microscopy (FN), no case was identified as non-pathologic (TN) and 01 case was incorrectly identified as pathologic (FP).

Table VIII. *Inter-observer agreement between conventional microscopy and the gold standard microscopic diagnosis in the identification of a pathologic process.*

Reference diagnosis CM	Pathologic	Non-pathologic
Pathologic	56	3
Non-pathologic	1	0

CM: conventional microscopy, K = 0.02

Table IX shows a Cohen's kappa score of **0.01** demonstrating slight agreement when the diagnosis by whole slide imaging was compared to the reference diagnosis in the investigation of a pathologic process. 58 cases were correctly identified by both modalities (TP), 01 case was falsely identified as non-pathology via whole slide imaging (FN), no case was identified as non-pathologic (TN) and 01 case was incorrectly identified as pathologic (FP).

Table IX. *Inter-observer agreement between whole slide imaging and the gold standard microscopic diagnosis in the identification of a pathologic process.*

Reference diagnosis WSI	Pathologic	Non-pathologic
Pathologic	58	1
Non-pathologic	1	0

WSI: whole slide imaging, K = 0.01

IV.3.1.2 Agreement rate for identification of the final pathologic diagnosis.

Table X shows the 42 accord cases and 18 disaccord when the diagnosis via whole slide imaging were compared to the diagnosis via glass microscopy in the identification of final pathologic diagnosis giving a concordance rate of 70**%.**

Table X. *Intra-observer concordance rate between whole slide imaging and conventional microscopy in the identification of the final pathologic diagnosis.*

Variable	**n**	**%**
Concordant	42	70
Discordant	18	30

WSI: whole slide imaging, CM: conventional microscopy.

Table XI shows the accord in 38 cases and disaccord in 22 cases when the microscopic diagnosis was compared to the reference diagnosis in the identification of the final pathologic diagnosis obtaining a concordance rate of **63.3%.**

Table XI. *Inter-observer concordance rate between conventional microscopy and the gold standard microscopic diagnosis in the identification of the final pathologic diagnosis.*

Variable	**n**	**%**
Concordant	38	63.3
Discordant	22	36.7

CM: conventional microscopy

Table XII shows the accord in 37 cases and disaccord in 22 cases when the whole slide imaging final diagnosis was compared to the reference diagnosis in the identification of the final pathologic diagnosis obtaining a concordance rate of **61.7%.**

Table XII. Inter-observer concordance rate between whole slide imaging and the gold standard microscopic diagnosis in the identification of the final pathologic diagnosis.

Variable	n	%
Concordant	37	61.7
Discordant	23	38.3

WSI: whole slide imaging

IV.3.2 Diagnostic performance

Table XIII shows the measures of diagnostic accuracy using whole slide imaging in the identification of pathologic processes. Having a sensitivity of 98.2%, a specificity of 33%, a positive predictive value of 96.6%, a negative predictive value of 100%.

Table XIII. *Sensitivity, specificity, positive predictive value, and negative predictive value of whole slide imaging in the identification of a pathologic process.*

Slide	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Digital slide	98.2	33.3	96.6	100

Figure 16 shows the area under receiver operating characteristic (ROC) curve of 0.151 demonstrating very poor discriminative power in differentiating a pathologic from a non-pathologic process using whole slide imaging.

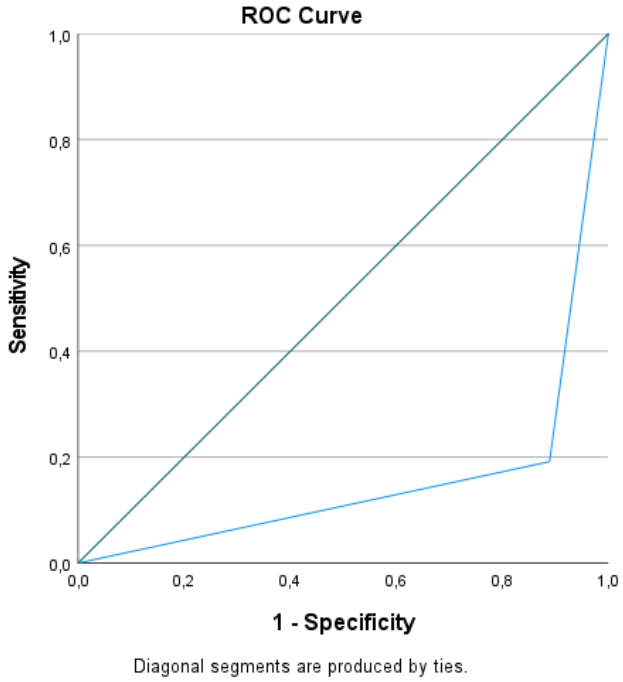

Figure 16: *Area under ROC curve for identification of a pathologic and non-pathologic process*

CHAPTER V: DISCUSSION

This was a diagnostic, descriptive case control study with the aim to assess the degree of agreement between whole slide imaging and conventional in the diagnosis of tissue biopsy specimens at HGOPY and CPC , as well as to evaluate the diagnostic performance of digital pathology and to evaluate the pros and cons of utilizing digital pathology as perceived by pathologist.

To achieve this, we selected 60 cases from the 02 pathology departments over a 5 months period extending from September 4th 2023 to January 26th 2024.We compared the pathologic diagnosis of the participating pathologist obtained via whole slide imaging to conventional microscopy and evaluated the measures of diagnostic accuracy.

Study Limitations

Our study was limited by the lack of reproducibility check of the baseline diagnosis where the most experienced pathologist's glass slide diagnosis was considered the reference standard. The study was equally limited by the small number of participating pathologists. Another limitation was that the reading pathologist didn't have access to relevant clinical information for each case and didn't have any prior training on the use of whole slide imaging for diagnostic purposes. Selection bias was another limitation in our study due to the inclusion of very few non-pathologic cases.

Diagnostic Results

The College of American pathologists recommends that the validation process for whole slide imaging system for diagnostic purposes should include a sample set of cases that reflects specimen types and diagnosis likely to be encountered during routine practice [40]. Benign breast lesions are the common amidst pre-menaupausal women with fibro-adenoma and fibrocystic breast changes being the most common[24,41].The cases included in our study were invasive ductal carcinomas (48.3%), invasive lobular carcinoma(5%), fibroscystic breast changes(16.6), ductal hyperplasia(8.3%), mastitis(5%), fibro-adenoma(8.3%), phylloides(1.6%), intraductal papilloma(1.6%), fat necrosis(3.3%) and non-pathologic(1.6%). This was similar to the cases included by Reyes et al. in 2014 with ductal carcinoma representing 44.7% of all cases[42]. Essiben et al. in 2013 equally found that ductal carcinoma accounted for 75.4% of the histologic

types of breast cancer in Cameroon[43]. This suggests that the cases chosen for our study could be representative of the commonly encountered breast lesions in our setting.

Concordance rate and degree of agreement

We obtained a concordance rate of 70% when the diagnosis via whole slide imaging was compared to that of conventional microscopy in the identification of the final pathologic diagnosis. This is similar to that obtained by Bomsembiante et al in 2019 who found a concordance rate range of 65%-78% for the 3 observers in their validation study for whole slide imaging for primary pathology diagnosis [44]. Alassiri et al in 2020 equally evaluated 60 pathology cases and found an overall concordance rate range of 68.3%-88.3% for the 04 observers in their study [2].This was different from what Mukhopadhyay et al in 2018 observed with an overall major concordance rate of 95.1% in their study. This difference could be attributed to the larger sample size of 1992 pathology cases and multiple observers (16) which could obscure the variability between individual observers in the aggregated results. In their study, the observers were more specialized in different subspecialties of pathology and underwent standard training for self-familiarization with WSI. Moreover, clinical information for each pathologic case to be reviewed was provided and observers were permitted to freely consult textbooks and other literature online [4]. Reyes et al in in 2014 equally obtained a higher concordance rate range of 96.3% - 98%. The significant difference in their study could be due to the fact that the participating pathologist were more experienced in surgical pathology (5-35 years) and had used whole slide imaging prior to the study though not for the purpose of primary diagnosis. Similarly, Babawale et al in 2021 equally had a higher concordance rate of 91.4% most likely due to the fact that participating pathologist were at least specialists in one or two subspecialties and were subjected to 03 series of pilot tests with whole slide imaging to develop knowledge and confidence in the use of digital pathology prior to the start of their validation study. Likewise, House et al in 2013 in a similar study equally had an overall concordance rate of 86% which was higher than that obtained in our study. This could be due to the fact that the washout period between the review of the 22 pathology cases by both modalities in their study was just 3 days so recall bias could account for the higher concordance rate obtained in their study [45]

The reading pathologist in our study had just 2 years of experience in surgical pathology and though had used whole slide imaging prior to our study for educative purposes had not used it for diagnostic purposes. We obtained an intra-rater concordance rate of 95% in the identification of a pathologic process and a concordance rate of 70% in the identification of the final pathologic diagnosis despite the fact that no pilot test on the use of whole slide imaging for diagnostic purposes was done neither was any relevant clinical information per case was made available in our study. Similar validation studies made sure participants had used Whole slide imaging for diagnostic purposes before or had taken part in a series of pilot tests prior to the start of their study to make familiar the digital system and improve the diagnostic accuracy of whole slide imaging [17,46]. This was corroborated by Nielsen et al in 2010 who observed a correlation between exposure to whole imaging and diagnostic accuracy. In their study 04 observers initially had as diagnostic accuracy 89%, 82%, 86% and 93% using WSI and after a 3 weeks period, the 4 observers were re-evaluated using WSI and were more accurate with 92%, 86%, 88% and 94% diagnostic accuracy respectively [47]. Showing that consecutive exposure to whole slide imaging could play a major role on diagnostic accuracy in the identification of the final pathologic diagnosis. Conversely, House et al in 2013 in their validation study for the use of WSI for cytopathology diagnosis had more accurate diagnosis amidst pathologist without digital pathology experience than among those with digital pathology experience [45].

The reference diagnosis considered in our study was the microscopic diagnosis of the most experienced pathologist. Nielsen et al in 2010 equally used the same model to consider the baseline diagnosis for their study [47]. A concordance rate of 63.3% for microscopy and 61.7% for whole slide imaging was obtained when the reading pathologist's diagnosis was compared to the reference diagnosis. This showed a 1.6% difference in favor of conventional microscopy demonstrating a minor superiority over whole slide imaging. Nevertheless, the Cohen's kappa score was necessary to assert this finding. The kappa (K) value showed an equal level of agreement of slight agreement between conventional microscopy with K value of 0.02 and that of whole slide imaging with K value of 0.01 when compared to the reference diagnosis. Likewise, Alassiri et al in 2020 found a 6% difference between whole slide imaging and traditional microscopy in favor of conventional microscopy but generated a kappa statistic for both modalities and obtained equal

levels of agreement with a K value of 0.14 for conventional microscopy and a K value of 0.20 for whole slide showing slight agreement for both diagnostic methods [2].

Diagnostic Performance

The sensitivity of whole slide imaging for the identification of pathologic processes was 98.2%. This is similar to that obtained by Bomsembiante et al in 2019 who had a sensitivity of 82 - 91% for their 3 observers though slightly lower than what obtained in our study. This could be due to the fact that the sensitivity in their study was on the bases of identifying neoplastic processes rather than a pathologic process as in our study. Nevertheless, they obtained a higher specificity of 63- 100% [44] compared to the 33.3% gotten in our study. This could be due to the fact that we had a high number of false positives and a small sample size making the specificity to be very sensitive to even small changes to the number of false positive. Nielsen et al in 2010 in a similar study obtained an overall positive predictive value and negative predictive value of 92% and 97% respectively for whole slide imaging in the identification of neoplastic processes [47] which are similar to the 96.6% positive predictive value and 100% negative predictive value obtained in our study.

Considering the fact the receiver operating curve (ROC) provides a more comprehensive assessment in distinguishing a pathologic from a non-pathologic process over the sensitivity and specificity [48], we then evaluated the area under the ROC curve for whole side imaging and obtained a value of 0.151 (95% confidence interval: 0.017 – 0.319). This indicates that our diagnostic modality is performing worse than a random classifier and has extremely low discriminative abilities. These low discriminative power could be due to the high false positive rate obtained in our study.

In view of the results obtained, it shows that whole slide imaging would not be appropriate as primary diagnostic tool in our setting despite the fact that many other studies carried out showed the feasibility, non-inferiority and the equivalent diagnostic accuracy of whole slide imaging as a primary diagnostic tool in pathology [2,4,17,42,44,46,49–52]. The present validation study followed the most recent guidelines by the American College of Pathologists [40].

CONCLUSION

VI. CONCLUSION

The objective of this study was to assess the degree of agreement between whole slide imaging and conventional in the diagnosis of tissue biopsy specimens at, as well as to evaluate the diagnostic performance of digital pathology and to evaluate the pros and cons of utilizing digital pathology as perceived by pathologist.

At the end of this study, we can state the following:

- The intra-rater and inter-observer agreement between whole imaging and conventional microscopy was moderate and slight respectively.
- The diagnostic performance of whole slide imaging for histopathological diagnosis was sub optimal in our setting. Familiarity with this diagnostic modality might improve results obtained in the study.

RECOMMENDATIONS

VI. RECOMMENDATION

Despite the limitations of our study we humbly recommend the following:

To pathologists, laboratories and hospitals

- To increase awareness and education on the principal benefits and applications of digital pathology.
- Permit small scale pilot projects in their hospitals and laboratories to demonstrate the feasibility of digital pathology in our setting.

To the Faculty of Medicine and Biomedical Sciences

- Institute and strengthen teachings on the applications of digital pathology amidst resident in surgical pathology.

To the scientific community

- To conduct more studies with a larger sample size and multiple observers with different levels of expertise to evaluate the accuracy of whole slide imaging as a diagnostic modality for histopathological diagnosis.

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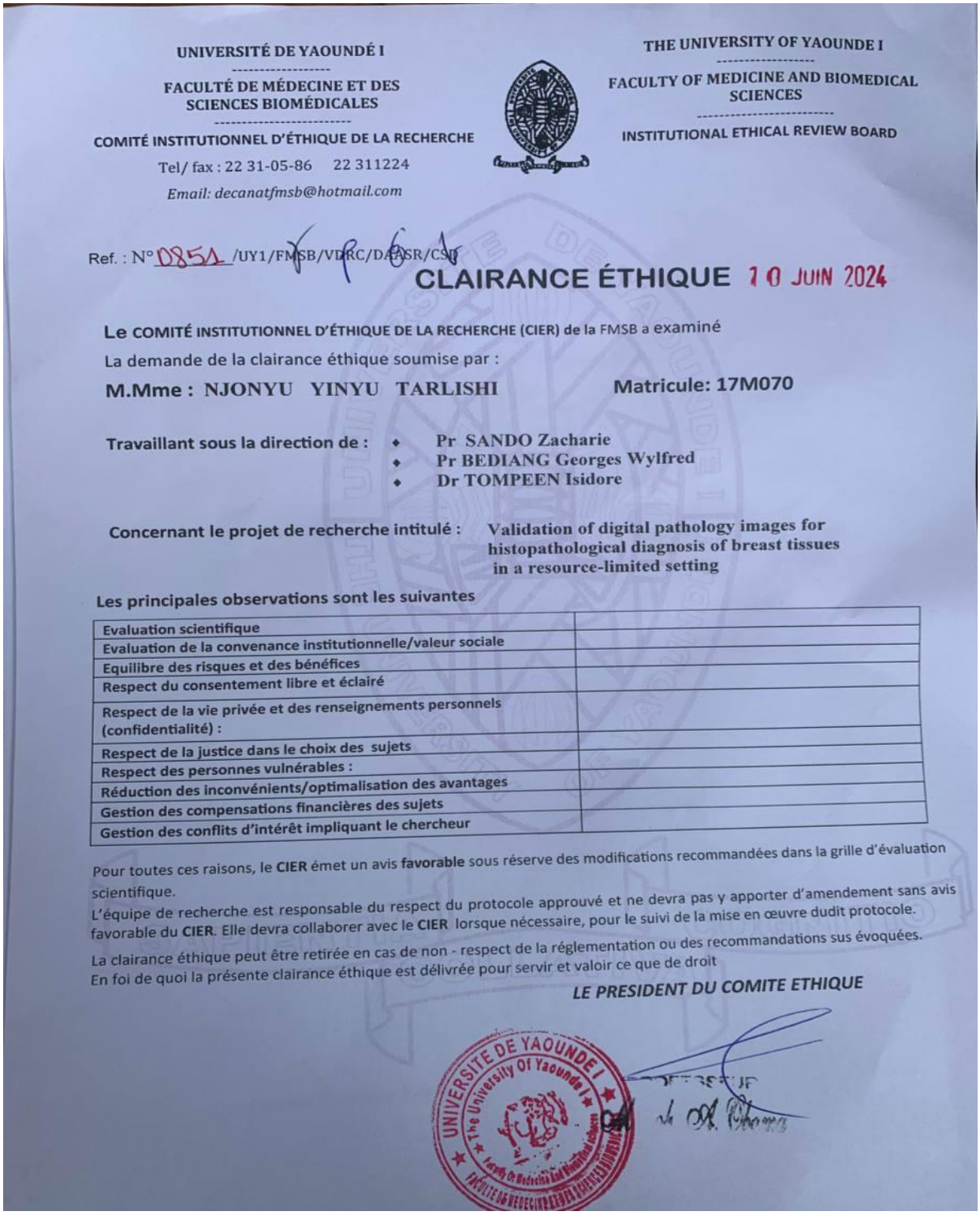
APPENDIX

Appendix 1. Ethical Clearance



UNIVERSITÉ DE YAOUNDÉ I
FACULTÉ DE MÉDECINE ET DES SCIENCES BIOMÉDICALES
COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE
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Email: decanatfmsb@hotmail.com

THE UNIVERSITY OF YAOUNDE I
FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES
INSTITUTIONAL ETHICAL REVIEW BOARD

Ref. : N° 0851 /UY1/FMSB/VDRC/DAASR/CSI

CLAIRANCE ÉTHIQUE 10 JUIN 2024

Le COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE (CIER) de la FMSB a examiné
La demande de la clairance éthique soumise par :
M.Mme : NJONYU YINYU TARLISHI Matricule: 17M070

Travaillant sous la direction de :
- Pr SANDO Zacharie
- Pr BEDIANG Georges Wylfred
- Dr TOMPEEN Isidore

Concernant le projet de recherche intitulé : Validation of digital pathology images for histopathological diagnosis of breast tissues in a resource-limited setting

Les principales observations sont les suivantes

Evaluation scientifique	
Evaluation de la convenance institutionnelle/valeur sociale	
Equilibre des risques et des bénéfices	
Respect du consentement libre et éclairé	
Respect de la vie privée et des renseignements personnels (confidentialité) :	
Respect de la justice dans le choix des sujets	
Respect des personnes vulnérables :	
Réduction des inconvénients/optimalisation des avantages	
Gestion des compensations financières des sujets	
Gestion des conflits d'intérêt impliquant le chercheur	

Pour toutes ces raisons, le CIER émet un avis favorable sous réserve des modifications recommandées dans la grille d'évaluation scientifique.
L'équipe de recherche est responsable du respect du protocole approuvé et ne devra pas y apporter d'amendement sans avis favorable du CIER. Elle devra collaborer avec le CIER lorsque nécessaire, pour le suivi de la mise en œuvre dudit protocole.
La clairance éthique peut être retirée en cas de non - respect de la réglementation ou des recommandations sus évoquées.
En foi de quoi la présente clairance éthique est délivrée pour servir et valoir ce que de droit

LE PRESIDENT DU COMITE ETHIQUE

Appendix 2. Research authorization from the Gyneco-obstetric and Pediatric Hospital Yaounde.

REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
MINISTERE DE LA SANTE PUBLIQUE
HOPITAL GYNECO-OBSTETRIQUE ET PEDIATRIQUE DE YAOUNDE
HUMILITE – INTEGRITE – VERITE – SERVICE

HGOPY
YGOPH

REPUBLIC OF CAMEROON
Peace-Work-Fatherland
MINISTRY OF PUBLIC HEALTH
YAOUNDE GYNAECO-OBSTETRIC AND PEDIATRIC HOSPITAL
HUMILITY – INTEGRITY – TRUTH – SERVICE

COMITE INSTITUTIONNEL D'ETHIQUE DE LA RECHERCHE POUR LA SANTE HUMAINE (CIERSH)

Arrêté n° 0977 du MINSANTE du 18 avril 2012 portant création et organisation des Comités d'Ethiques de la Recherche pour la santé Humaines. (CERSH).

AUTORISATION N°603 /CIERSH/DM/2024

CLAIRANCE ETHIQUE

Le Comité Institutionnel d'Ethique de la Recherche pour la Santé Humaine (CIERSH) a examiné le 24 janvier 2024, la demande d'autorisation et le Protocole de recherche intitulé « **validation of digital pathology images for histopathological diagnosis of breast tissues in a resouces-limited setting** » soumis par l'étudiant NJONYU YINYU TARLISHI.

Le sujet est digne d'intérêt. Les objectifs sont bien définis. La procédure de recherche proposée ne comporte aucune méthode invasive préjudiciable aux participants. Le formulaire de consentement éclairé est présent et la confidentialité des données est préservée. Pour les raisons qui précèdent, le CIERSH de HGOPY donne son accord pour la mise en œuvre de la présente recherche.

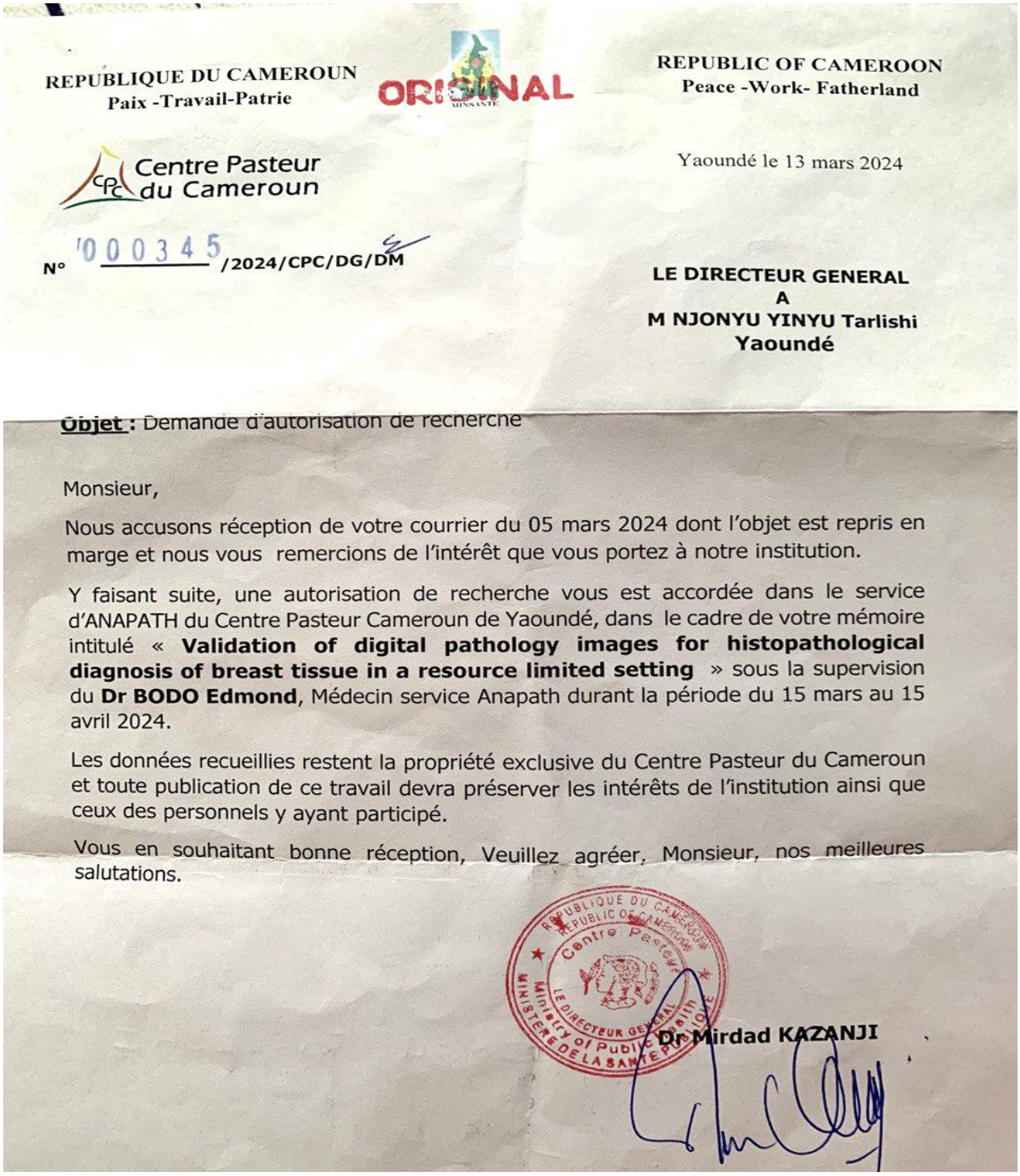
NJONYU YINYU TARLISHI devra se conformer au règlement en vigueur à HGOPY et déposer obligatoirement une copie de ses travaux à la Direction Médicale de ladite formation sanitaire.

Yaoundé, le 08 FEV 2024

LE PRESIDENT

Prof MBU Robinson
Directeur Général
HGOPY

Appendix 3. Research authorization from Centre Pasteur Cameroon.



REPUBLIQUE DU CAMEROUN
Paix -Travail-Patrie

ORIGINAL

REPUBLIC OF CAMEROON
Peace -Work- Fatherland

Centre Pasteur du Cameroun

Yaoundé le 13 mars 2024

N° 000345 /2024/CPC/DG/DM

LE DIRECTEUR GENERAL
A
M NJONYU YINYU Tarlishi
Yaoundé

Objet : Demande d'autorisation de recherche

Monsieur,

Nous accusons réception de votre courrier du 05 mars 2024 dont l'objet est repris en marge et nous vous remercions de l'intérêt que vous portez à notre institution.

Y faisant suite, une autorisation de recherche vous est accordée dans le service d'ANAPATH du Centre Pasteur Cameroun de Yaoundé, dans le cadre de votre mémoire intitulé « **Validation of digital pathology images for histopathological diagnosis of breast tissue in a resource limited setting** » sous la supervision du **Dr BODO Edmond**, Médecin service Anapath durant la période du 15 mars au 15 avril 2024.

Les données recueillies restent la propriété exclusive du Centre Pasteur du Cameroun et toute publication de ce travail devra préserver les intérêts de l'institution ainsi que ceux des personnels y ayant participé.

Vous en souhaitant bonne réception, Veuillez agréer, Monsieur, nos meilleures salutations.

Dr Mirdad KAZANJI

Appendix 4: Data collection sheet.

Case number	1.Pathologic ☐ 2.Non-pathologic ☐	**If pathologic (1)** A. **Neoplastic**(specify) ☐ A1 .Benign ☐ A2. Malignant ☐ B**. Non-neoplastic** ☐	**If non-neoplastic (B)** B1. **Inflammatory** ☐ (specify) 1 .Mastitis ☐ 2. Fat necrosis ☐ 3 .Mammary duct ectasia ☐ 4. Others ☐ (specify) B2**. Non-inflammatory** ☐ (specify) 1. Ductal epithelial ☐ hyperplasia 2 .Sclerosing adenosis ☐ 3 .Breast cyst ☐ 4 .Apocrine metaplasia ☐ 5 .Others ☐ (specify)	**If Benign neoplastic (A1)** 1 .Fibro-adenoma ☐ 2. Lobular carcinoma insitu ☐ 3. Intraductal papilloma ☐ 4. Phyllodes tumor ☐ 5. Fibrocystic breast changes 6. others ☐ (specify) **If Malignant neoplasm (A2)** **A21 Invasive** ☐ (specify) 1. Invasive Ductal carcinoma ☐ 2. Invasive lobular carcinoma ☐ 3. Inflammatory Breast cancer ☐ 4. others ☐ (specify) **A22 Non-invasive** ☐ 1.Non-invasive ductal carcinoma ☐ 2. Others ☐ (specify)