Master Thesis

THE FUTURE OF DIGITAL PATHOLOGY FOR CLINICAL RESEARCH IN BIOBANKING

submitted by

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Abstract in German

Diese Abschlussarbeit wurde erstellt, um die Auswirkungen der digitalen Pathologie auf Biobanking und klinische Forschung zu bewerten. Auf der Grundlage einer Literaturrecherche untersucht diese Studie die technologischen Vorteile der digitalen Pathologie gegenüber traditionellen Methoden und wie sich diese Vorteile auf Biobanking-Anwendungen auswirken.

Die digitale Pathologie bietet dank hochauflösender Bildgebungstechnologien und computergestützter Analysewerkzeuge eine höhere Genauigkeit, Geschwindigkeit und Fernzugriffsmöglichkeiten in diagnostischen Prozessen. Gleichzeitig eröffnet ihre Integration mit Anwendungen der künstlichen Intelligenz neue Möglichkeiten in Bezug auf die Klassifizierung von Krankheiten, die Analyse von Biomarkern und Entscheidungsunterstützungssysteme. Diese Entwicklungen ermöglichen es, in Biobanken gesammelte Gewebeproben in eine digitale Umgebung zu übertragen und sie in eine langfristige, sichere und wiederverwendbare Dateninfrastruktur umzuwandeln.

In dieser Studie wurden nach 2010 veröffentlichte Quellen unter thematischen Überschriften bewertet; technische Entwicklungen, die Integration mit künstlicher Intelligenz, ethische und rechtliche Vorschriften sowie klinische Forschungsanwendungen wurden als grundlegende Kategorien behandelt. Die Bedeutung der Datenstandardisierung, der Qualitätskontrollprotokolle und der Einhaltung internationaler Vorschriften im Prozess der Verbreitung der digitalen Pathologie wurden hervorgehoben.

Die digitale Pathologie ist nicht nur eine technologische Veränderung, sondern stellt eine umfassende Systemtransformation dar, die viele Komponenten betrifft, von klinischen Entscheidungsmechanismen bis hin zur Forschungsinfrastruktur. Damit diese Transformation effektiv umgesetzt werden kann, müssen die institutionelle Bereitschaft, die ethische Verantwortung und die technische Infrastruktur gemeinsam bewertet werden.

Abstract in English

This thesis study was prepared to evaluate the impact of digital pathology on biobanking and clinical research. Based on a literature review, this study examines the technological advantages offered by digital pathology over traditional methods and how these advantages relate to biobanking applications.

Digital pathology provides higher accuracy, speed, and remote access in diagnostic processes thanks to high-resolution imaging technologies and computer-assisted analysis tools. At the same time, its integration with artificial intelligence applications offers new opportunities in terms of disease classification, biomarker analysis, and decision support systems. These developments make it possible to transfer tissue samples collected in biobanks to a digital environment, transforming them into a long-term, secure, and reusable data infrastructure.

In this study, sources published after 2010 were evaluated under thematic headings; technical developments, integration with artificial intelligence, ethical and legal regulations, and clinical research applications were addressed as basic categories. The importance of data standardization, quality control protocols, and compliance with international regulations in the process of disseminating digital pathology were emphasized.

Digital pathology is not merely a technological change; it represents a comprehensive system transformation that affects many components, from clinical decision-making mechanisms to research infrastructure. For this transformation to be effectively implemented, institutional preparedness, ethical responsibility, and technical infrastructure must be evaluated together.

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Glossary and Abbreviations

AI	Artificial Intelligence
BBMRI	Biobanking and BioMolecular Resources Research Infrastructure
CE IVD	Conformité Européenne In Vitro Diagnostics
DL	Deep Learning
DICOM	Digital Imaging and Communications in Medicine
FAIR	Findable, Accessible, Interoperable, and Reusable
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FIBI	Fluorescence Imitating Brightfield Imaging
GDPR	General Data Protection Regulation
H&E	Hematoxylin and Eosin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ISBER	International Society for Biological and Environmental Repositories
ISO	International Organization for Standardization
LIS	Laboratory Information System
MIABIS	Minimum Information About BIobank data Sharing
ML	Machine Learning
RECs	Research Ethics Committees
SOP	Standard Operating Procedure
SVM	Support Vector Machines
TI	Technical Integration
VNA	Vendor Neutral Archive
WSI	Whole Slide Imaging

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1 INTRODUCTION

Histopathology is a scientific discipline based on the microscopic examination of cellular-level morphological structures and has long been considered one of the most reliable methods in clinical diagnosis. The advancement of digital pathology (DP) has started the replacement of conventional diagnostic methods by next-generation digital diagnostic technologies. These methods are based on computerized analysis of high-resolution digital images. Digital pathology enables not only the digitalization of images but also the integration of advanced technologies such as artificial intelligence (AI), machine learning (ML), and deep learning (DL). This offers significant advantages for objectivity, reproducibility, and efficiency in pathological assessments. (1)

This technological development presents significant opportunities, particularly for clinical research in the field of biobanking. Biobanks are systematically organized units that store biological materials, tissue, blood, and DNA samples, as well as clinical and demographic data related to these samples, for long periods.(2) The digitization of histopathological preparations and their storage in biobanks through digital pathology applications has facilitated the discovery of biomarkers, the creation of clinical prediction models, and the optimization of targeted treatment strategies by evaluating these materials with high-end analysis techniques. (3)

In particular, the increasing use of whole-slide imaging (WSI) systems enables pathologic evaluations to be performed remotely and simultaneously. Also, the use of artificial intelligence algorithms incorporated into clinical decision support systems increases diagnostic accuracy and reduces the workload of pathologists. However, technical limitations (e.g., focal plane losses, data transfer speed, storage capacity) and practical challenges, such as user habits, which are encountered during the process of digital pathology diffusion, necessitate careful planning in the integration of the system. (4)

Not only technical but also ethical and legal aspects are important in the integration of digital pathology into clinical research. The 'black box' nature of AI-supported decision-making systems raises transparency and accountability issues in decision-making processes. Ethical concerns in research include patient privacy, data security, informed consent and algorithmic bias. (5) Especially when

the role of AI systems in medical decisions is unclear, the question of who is responsible remains unanswered.

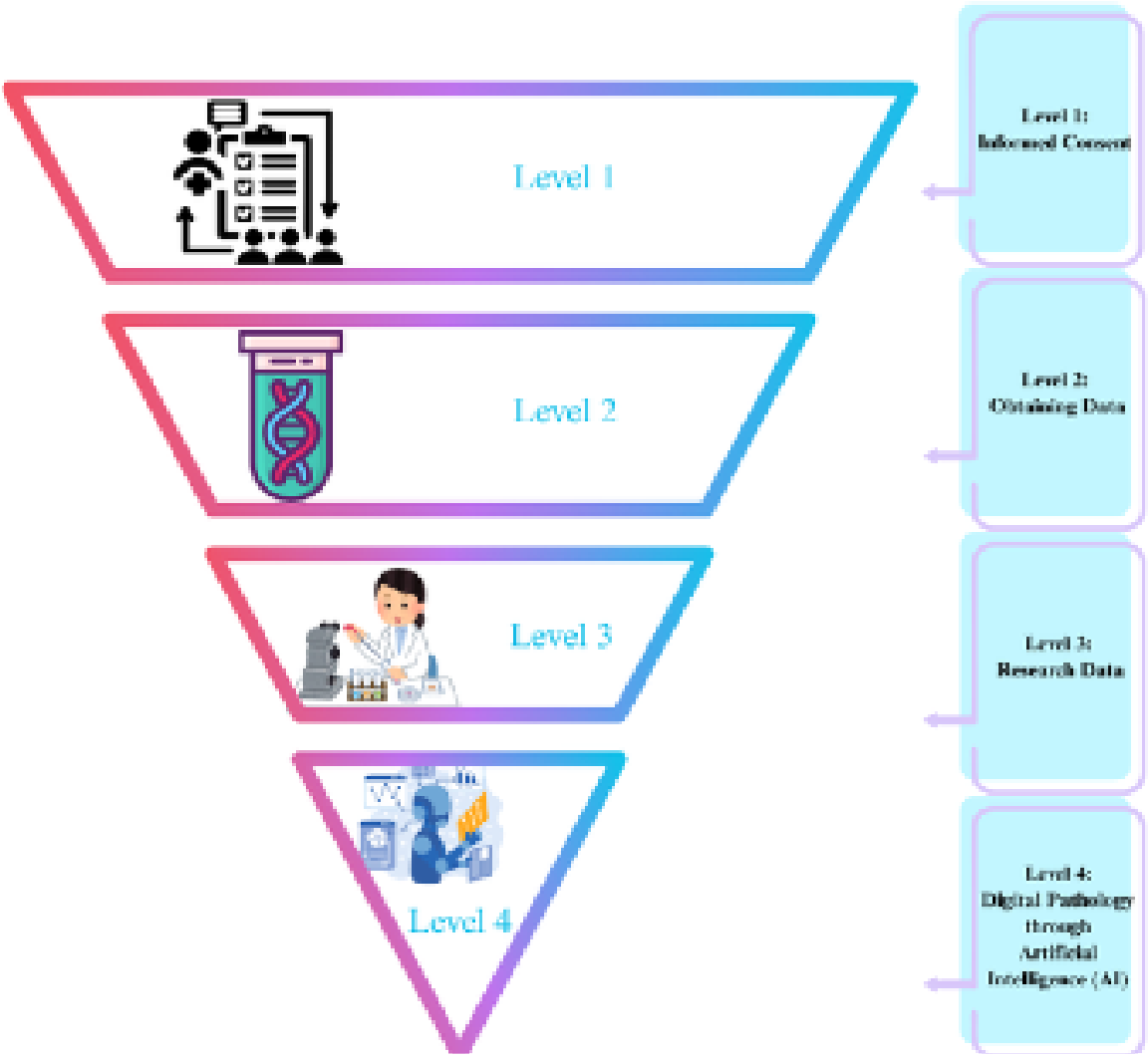


Figure 1. This schematic representation explains how artificial intelligence, combined with digital biobanking, offers a layered approach to cancer research. The initial stage of the process (Level I) begins with the patient giving informed consent. The next stage (Level II) involves the collection of biospecimens and the implementation of laboratory information management systems. The data obtained in Level III, where the research environment is shaped, forms the basis for scientific studies. At the lowest level (Level IV), the process involves digitizing tissue slides with AI-supported analysis and interpreting large datasets using deep learning algorithms. Figure adapted from Frascarelli et al. (2023) and created with Canva.

2 THEORETICAL BACKGROUND

2.1 Traditional Pathology

Traditional pathology depends on examining tissue samples through a microscope, where pathologists analyze cellular structures and patterns to formulate diagnostic conclusions. This subjective method can differ among observers, resulting in inconsistent outcomes. Tasks like counting certain cell types (e.g., mitotic cells or Ki-67 positive cells) are often repetitive and susceptible to human error. (6,7) While these techniques are cost-efficient, readily accessible, and suitable for FFPE samples, their reliance on visual assessments leaves them exposed to inter-observer variability, which can affect diagnostic precision and patient treatment results.

2.2 Digital Pathology

Digital pathology, also known as whole slide imaging (WSI), is the process where glass microscope slides are transformed into digital format through high-resolution scanning. This technology offers high-level digital images that can be analyzed, stored and shared. In this way, the pictures can be used for diagnosing, research, and as educational materials. With the help of AI tools, such as deep learning, and computer-assisted image analysis and pattern recognition, digital pathology promotes reproducibility and collaboration in pathology even more. It also allows pathologists to review slides remotely and additionally to get second opinions. Regulatory approval, such as FDA or CE IVD, is usually the requirement for the use of these technologies for diagnostic purposes. (6–8)

2.3. Artificial Intelligence (AI)

The use of artificial intelligence (AI) algorithms facilitates the analysis of images through computer programs, leveraging available technological capabilities. This analysis processes data outputs and applies statistical methods to model the data

in a way that progressively adapts (‘learns’) to fit a defined outcome, deriving insights and generating findings. (9)

Artificial intelligence (AI) applications in pathology increase quantitative accuracy and can improve clinical workflows by analyzing multiple biomarkers in histopathology images using data in algorithms with machine learning methods.

The potential of precision medicine has become more analyzable thanks to the emergence of artificial intelligence. Analyzing the vast amounts of data produced in the era of genome sequencing has made it possible to integrate not only these genomic and genetic data but also the massive datasets that include all medical record data and digital imaging, such as radiology and pathology images. (10)

2.4 Biobank

Biobanks are institutional infrastructures where biological samples from humans, animals, plants, and microorganisms are systematically collected, processed, stored, and made accessible for scientific research. These structures play a fundamental role in preserving biological diversity and supporting health-related research. (11,12)

Biobanks are mostly focused on handling human biospecimens. In that case, biological samples can be stored from patients with different diseases; thus, they are sources of materials for the study of disease initiation. Human biobanks are organized to include not only biological samples such as blood, plasma, serum, tissue, and DNA, but also donor-related information such as demographic data, clinical records, medical history and lifestyle details, by way of a good collection method, the processing of the sample, and storage of the sample protocols. Biobanks play a critical role in translational and personalized medicine by providing high-quality samples and associated data sets, which are essential for the development of new diagnostic markers and personalized treatment approaches. The purpose is to support research and foster innovative disease diagnosis and treatment methods. (13,14)

Animal biobanks collect, process, and store blood and tissue samples from a wide range of animal species, aiming to preserve the genetic material of these species. For instance, the Cornell University Veterinary Biobank supports research worldwide by preserving animal-derived tissues for long-term storage, thereby contributing to advancements in both veterinary and human medicine. By bridging the gap between animal and human health, these biobanks foster interdisciplinary collaborations and accelerate researchers' projects, ultimately promoting progress in both animal and human health. (15)

Environmental biobanks focus on the preservation of soil, water, and microbial samples. These samples are utilized in studies that include monitoring environmental changes, tracking biodiversity, and conducting microbiome research. Initiatives like the proposed National Microbiome Biobank in the United Kingdom demonstrate the growing potential in this field. (16)

2.5 Clinical Research

Clinical research is a means of advancing our knowledge of human diseases, finding prevention and treatment, and improving our health. (17) Clinical research is performed to e.g. analyze the functions and characteristics of how drugs and treatments interact with the body. (18) Pre-clinical research is more about the safety of the drugs being investigated but only through laboratory and animal-based research. However, even these cannot replace the testing on humans. (19)

2.6 The Role of Biobanks in Digital Pathology

Biobanks are known as repositories for storing biospecimens such as tissues, blood, and DNA. They are evolving to play a transformative role in digital pathology.

Biobanks provide critical data that feed machine learning models, aiding in the development of more accurate diagnostic and predictive tools. (6)

Early detection of cancer is crucial for increasing survival rates, as it allows for timely treatment before the disease progresses. Modern advances in technology

have made it possible to detect early signals of cancer through various diagnostic tools and techniques, many of which can be accessed remotely, enabling early intervention remotely. (20)

Computer-assisted diagnostics play a key role in this process, which uses artificial intelligence and machine learning algorithms to analyze medical data such as imaging glass microscope slides with extraordinary precision. These systems can detect the smallest changes or abnormalities that may indicate early stages of cancer, even before symptoms appear. (6) Additionally, telemedicine platforms make it easier for patients to consult with specialists, review diagnostic results, and receive personalized treatment plans remotely. (21)

Essentially, remote and AI-powered diagnostic tools have the potential to revolutionize the early detection of cancer, making it faster, more accessible, and ultimately more effective at saving lives.

2.7 Histopathological Image Analysis and AI Integration

2.7.1 Digital image processing

A major development in the field occurred during the 1990s with the advent of whole-slide imaging (WSI) (6). More recently, digital pathology whole-slide images have been approved by the FDA for use in primary diagnoses within clinical surgical pathology practices. (21). A whole-slide imaging (WSI) system includes the digitization of slides with entire tissue sections that are fixed in formalin and embedded in paraffin (FFPE) and stained with hematoxylin and eosin (H&E). In most cases, a special scanner is used to produce a high-resolution digital image of the whole slide. This technology is widely used in pathology and biomedical research instead of traditional microscopy. (21)

There are few key points about WSIs:

1. High resolution

   Whole-slide imaging (WSI) technology has the capacity of producing extremely precise images of tissue, where the pathologists can zoom in on something at the cellular level in detail. This device is a high-resolution technology, which can rapidly digitize traditional glass slides at resolutions as fine as 0.23–0.25 μm per pixel. (6)

2. Entire tissue sample
   Unlike traditional imaging methods that capture only specific regions of interest, WSIs encompass the entire slide, ensuring no part of the sample is missed.
3. Digital format
   These images are stored in digital formats, making them easy to share, annotate, and analyze using computer software.
4. Applications

- Pathology: For diagnosis, education, and consultation.
- Research: In studying diseases, drug development, and artificial intelligence training for medical imaging.
- Telemedicine: Enabling remote consultations and second opinions.

In addition to high-resolution imaging capabilities, one of the key elements in digital pathology is the use of standardized image formats. The DICOM (Digital Imaging and Communications in Medicine) format, long widely used in radiology, is now increasingly integrated into digital pathology workflows. Unlike proprietary file formats used by different scanner manufacturers, the DICOM format provides interoperability between systems and enables structured metadata storage. This allows for easier archiving, access, and analysis of images across platforms. DICOM adoption significantly supports data sharing, consistency, and long-term availability, particularly for multicenter studies or AI model development. (22,23)

2.7.2 Automated image analysis

AI is rapidly transforming the field of pathology, where it is now being used for image analysis and segmentation. It increases the efficiency of reporting by reducing processing times and providing more precise assessments of feature characteristics. By automating repetitive and time-consuming tasks, AI frees pathologists to concentrate on more intricate cases and effectively manage increasing workload demands. (22)
In digital pathology, AI applications are focused primarily on automating more

complex tasks, saving pathologists time and enabling them to have more time to think about diagnosis, especially in cases involving complex disease presentations. Moreover, AI supports oncologists by helping to develop prognostic tools to assess disease severity and outcomes. These tools also help to predict therapy responses, contributing to improved patient management and treatment planning. (25)

Additionally, the use of AI in digital pathology contributes to early diagnoses and improves patient care by optimizing therapeutic responses and outcomes. It provides an essential resource in modern pathology, facilitating workflows while addressing critical diagnostic and prognostic challenges. (25)

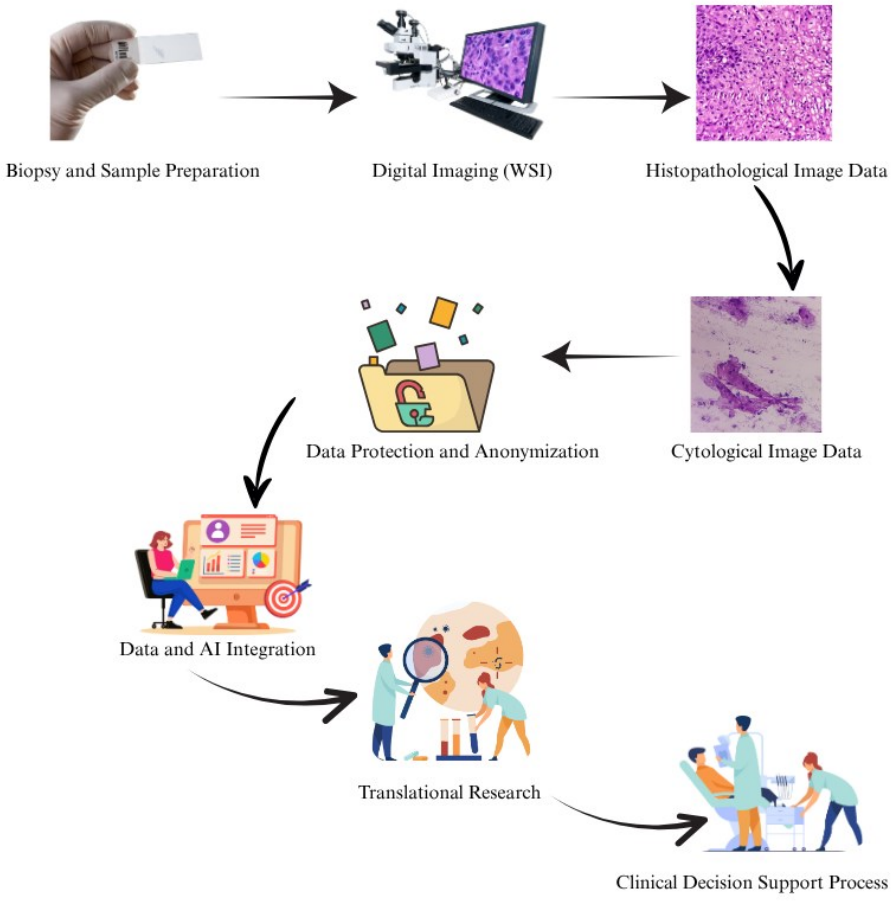


Figure 2. An overview of the digital pathology workflow that combines the collection of histopathological images, the handling of anonymized data, and artificial intelligence for automated image analysis. By enhancing diagnostic

efficiency and accuracy, the procedure facilitates informed clinical decision-making and supports translational research.

2.8 Biobank and Data Management

2.8.1 Diversity of Data and AI Integration

Biobanking involves a richness of data types, including but not limited to clinical, genomic and imaging data, which complicates the process of harmonizing data standards. This diversity of targets reinforces the need for a unified standardization approach. (24)
Recent AI Developments–The last few years have seen exponential growth in AI techniques, including the analysis of large genomic datasets and concurrent integration of disparate medical data such as electronic health records, radiology images, and pathology images. Such integration improves the ability to extract insights from the large and heterogeneous data generated in contemporary healthcare and research. (10)

2.8.2 Standardization and Quality Assurance

ISO standards and Standard Operating Procedures (SOPs) are essential for biobank operations, providing consistency in practices and ensuring high-quality data management. SOPs specify the processes for data collection, storage, curation, and documentation, while quality assurance protocols ensure compliance with these standards through training and audits. These measures are crucial for preserving data quality, reproducibility, and adherence to regulatory requirements. (14)
Standardization in data entry, documentation, and storage is important for accuracy and interoperability. By using clear guidelines, data dictionaries, and templates, uniform data capture is supported, and data validation against standardized vocabularies further increases reliability. (14)
Without standard protocols, inconsistencies in the management of samples or data can compromise the quality of samples and the reproducibility of research. Long-term storage and standardized data formats are critical to maintaining sample stability and integrating diverse datasets. (24)
Compliance with ISO specifications such as ISO 20387:2018 provides a comprehensive framework for biobanking. These standards ensure the integrity, traceability and reliability of biological materials and related data by addressing technical specifications, quality

control and ethical conduct. By implementing SOPs and international standards, biobanks can assure sample quality and data integrity, supporting meaningful and reproducible research results. (24)

2.9 Ethical, Legal and Regulatory Considerations

The ethical and legal aspects of data diversity involve addressing challenges related to privacy, consent, and ownership. Aligning ethical standards and regulatory requirements across jurisdictions is crucial for ensuring compliance with laws such as GDPR and HIPAA. Establishing data governance frameworks, privacy protections, and security measures helps ensure adherence to these regulations while maintaining data quality and integrity. (14)

2.9.1 Informed Consent and Data Use

In recent years, public awareness of biobanks and the secondary use of biological samples have increased, leading to ethical and legal discussions about the informed consent process. The use of samples without informing the participants, such as the HeLa cell line, which was on the New York Times bestseller list, has attracted public attention, but it has also revealed that there is still a serious lack of knowledge about the general nature of biomedical research. (11) Although the basic ethical principles regarding the use of human-derived biological materials in the research process are framed by international texts such as the Declaration of Helsinki, differences between countries and inconsistencies in legal regulations make it difficult to establish standard practices. (26) There is minimal agreement regarding the reporting of individual research findings to participants, the conditions under which this should occur, and the responsible parties for such communication. However, some researchers and ethics advocates argue that participants have the right to receive information that could affect their health and life decisions. (11) The purposes of biobanks are not specific to a particular research study. Since there are no restrictions, the consents accepted in the Helsinki Declaration are specific to a particular study and do not fully meet the needs in the field of biobanking. (26,27) Due to these challenges, broad consent, a

type of consent that has been developed and is frequently preferred, allows donors to give general consent for their health data and biospecimens to be used in various future medical research studies. (28)

2.9.2 Data Privacy and Protection

Among the most critical ethical challenges in biobanking are data privacy and protection. Genetic materials and clinical data stored in biobanks, which include human DNA, affect not only individuals but also their families and the entire society. (26,29) Techniques such as anonymization, coding, and pseudonymization are necessary to protect sensitive information. (27)
Digital pathology and artificial intelligence (AI)-supported analyses significantly contribute to the identification of clinically meaningful biomarkers; however, these potential benefits face various ethical and legal limitations within the framework of personal data privacy and data protection regulations. According to the European Union General Data Protection Regulation (GDPR), even if they do not fully contain identifiable information, whole-slide images (WSIs) are considered personal data due to the possibility of individuals' identities being deduced when combined with other datasets.
The GDPR is based on the idea of data minimization, which is reflected in its restrictions regarding the reuse of personal data in ways that are not consistent with its original purpose. However, the efficacy of AI models, more specifically deep learning algorithms, depends on the availability of significant volume, diverse and long-term patient data. A situation that creates tension between AI's "data hunger" and the restrictive norms imposed by data ethics and regulations. Furthermore, the incorporation of clinical data or long-term outcome information into WSIs enhances the model's diagnostic capabilities. However, this practice entails a risk of reuse under GDPR, as the data is utilized beyond the context in which it was initially collected. (29)

2.9.3 Artificial Intelligence and Accountability

Artificial intelligence (AI) systems offer major advantages in digital pathology by automating and accelerating diagnostic processes. However, the "black box" nature of AI, i.e., its opaque decision-making processes, raises important ethical and legal concerns. The issue of responsibility when an AI system makes an

incorrect decision remains a significant concern. Therefore, it is suggested that AI should support clinical decisions rather than completely replace them. (5,30) Furthermore, the variety and representativeness of training datasets are also essential for reducing bias and preventing discriminatory results. To guarantee patient safety and accountability, regular ethical assessments, clinical confirmation, and ongoing updates are crucial. (31)

2.9.4 Commercialization and Data Use

The field of computational pathology, which is linked to companies with scanning technology, aims to generate profits from the data collected. These partners are referred to as commercial stakeholders. Stakeholders make a profit from using tissue. (29) Some studies have shown that public confidence in biobanks has declined due to commercialization. (26)

2.9.5 Regulatory Compliance and Ethical Committees

Digital pathology systems must meet a number of national and international regulatory standards in order to be used for clinical diagnosis. In the United States, FDA approval is mandatory, whereas in Europe, CE-IVD certification and ISO 15189 quality accreditation are standard requirements. (1)

Furthermore, all clinical and research applications are subject to review and approval by Research Ethics Committees (RECs). Despite the absence of a specific legal framework governing biobanking in Turkey, international instruments, such as the Council of Europe's Oviedo Convention, can serve as significant reference points. The absence of a specific legal framework creates gaps in the protection of participant rights and the transparency of research. (26)

2.10 Benefits and Challenges of Digital Pathology in Biobanking

The integration of digital pathology (DP) with whole-slide imaging (WSI) technology has had a profound impact on the work of pathologists and the contribution of tissue samples stored in biobanks to clinical and translational research. While this transformation has introduced numerous significant

advantages, it has also brought new challenges that must be carefully addressed. One of the most notable advantages of WSI-based digital pathology is the significant increase in speed and efficiency in the diagnostic workflow. High-capacity scanners can convert tissue sections into high-resolution digital images in a few minutes; these images can be viewed and evaluated remotely. *"Two scanners, Philips IntelliSite Pathology Solution (PIPS) (Philips, Amsterdam, Netherlands) and Leica Aperio AT2 DX System (Leica Biosystems, Buffalo Grove, Illinois, USA), are approved by the FDA for review and interpretation of digital surgical pathology slides prepared from biopsied tissue."* (32) Digital images stored in a central archive system provide a robust infrastructure for research conducted in collaboration with biobanks, enabling long-term accessibility and traceability of data.

Digital pathology will provide a solution to long-standing problems such as differences in opinion among pathologists using conventional microscopes. Diagnostic consistency and reproducibility can be greatly improved through the standardization of image formats and the use of digital analysis tools. (9)

The preservation of digital slide data without corruption and organized accessibility is provided by vendor-neutral archiving systems (VNA) and smart storage solutions. It is crucial to integrate these systems with health informatics infrastructures for large-scale research, such as biomarker discovery. This enables histological data to be matched with clinical information. The role of digital pathology in biobanking is expanding with the use of digital archiving and storage systems. (32,33)

Despite all these advantages, the transition to digital pathology brings with it some significant challenges. During the first phase of implementation, factors such as high scanner costs, storage infrastructure, and software integration cost a large amount of money. Also, some countries still have limited legal regulations about using WSI for diagnosis, which can make it harder to use WSI in clinical settings. Managing large image files also brings up new issues like patient safety and interoperability, posing challenges for network infrastructure and data security. (33)

Finally, the human factor should be considered. Pathologists need to be trained to adapt to digital workflows, and the institutional culture is expected to be ready for

digital diagnosis. Resistance to change, concerns about diagnostic accuracy, and technological problems may be encountered. (9,33)

In conclusion, digital pathology has the potential to improve diagnosis accuracy, ensure research can be repeated, and promote global collaboration when combined with advanced archiving, AI-based analysis, and biobanking infrastructure. However, to fully realize this potential, everyone must collaborate to overcome technical, legal, and organizational challenges. (9,32,33)

3 AIM AND GOALS

The aim of this master's thesis is to evaluate the transformative impact of digital pathology on biobanking infrastructures and clinical research. This study investigates how the transition from traditional microscopy to high-resolution digital imaging (Whole Slide Imaging (WSI)), computer-assisted analysis (Artificial Intelligence (AI)), specifically analyzing how these advancements enhance diagnostic accuracy, reproducibility, and workflow efficiency compared to traditional methodologies.

In addition, the thesis explores how biobanks support these digital advancements by providing high-quality biospecimens, well-annotated clinical data, and long-term storage infrastructures essential for AI-driven research. The integration of digital pathology with biobank resources is also assessed in relation to biomarker discovery, strengthening translational research, and contributing to the development of precision medicine.

Furthermore, the study considers key requirements for data standardization and the ethical implications of digital workflows, including data privacy and informed consent. Key variables include digital pathology, biomarker identification, potential of discoveries in medicine and regulatory challenges. A literature review was performed to evaluate outcomes, identify existing limitations, and future perspectives for implementing digital pathology within modern biobanking systems.

4 METHODS

This master's thesis is designed as a literature review to examine the impact of digital pathology on biobanking and clinical research. The literature review comprehensively addresses the technical aspects of digital pathology, its integration with artificial intelligence, and its ethical and legal framework, as well as its applications in biobanking practices.

4.1 Literature Search Strategy

The literature search process was utilized using academic databases such as PubMed, Science Direct, Google Scholar, FDA, and European regulatory websites, as well as various institutional resources (e.g., Cornell Biobank). The study evaluated peer-reviewed articles, review articles, reports, and guidance materials that were published between 2010 and 2025.

The keywords used during the search were as follows:

“digital pathology,” “biobanking,” “artificial intelligence,” “whole slide imaging,” “data ethics,” “computational pathology,” “dynamic consent,” “GDPR and AI,” “translational research,” and “early cancer detection.”
Boolean operators (AND/OR) were used to refine search outputs.

4.2 Inclusion and Exclusion Criteria

Inclusion criteria:

- The article is written in the fields of digital pathology, biobanking, or artificial intelligence
- Published after 2010
- Written in English or Turkish
- A formal publication, a peer-reviewed journal, or an institutional report

Table 1. Inclusion and Exclusion criteria of the literature review

Inclusion criteria	**Exclusion criteria**
Relevant to the research question Published in English or Turkish Published 2010 or later An official publication, a peer-reviewed journal, or an institutional report	Other languages than English and Turkish Publications before 2010 Articles that do not answer the research question

4.3 Study Selection and Data Analysis During

Search engine: PubMed

• Search Strategy: "digital pathology" AND "biobanking"
Filters: Review, 2010-2025, English/Turkish, Full text
Result: 18 hits
Selected: 4 sources
Taken together, these resources (3, 10, 13, 20) demonstrate the transformative impact of digital pathology on biobanking practices. They were chosen to present a holistic view of the field's technological and methodological evolution, specifically bridging the gap between improved imaging techniques and robust quality assurance. Furthermore, they underscore the essential role of AI integration and data management in modernizing how histopathological images are analyzed within biobanks.

• Search Strategy: Digital pathology and "challenges" "biobanking" as "review"
Filters: Review, 2010-2025, English/Turkish, Full text
Result: 2 hits
Selected: 2 sources
These resources (10, 23) discuss both the opportunities and challenges of data management in digital biobanks. They also serve as a primary resources for explaining the challenges and information about the DICOM format in digital pathology.

• Search Strategy: "digital pathology" [Title] AND "artificial intelligence"[Title] and "AI" and "machine learning" and computational pathology as "review"
Filters: Review, 2010-2025, English/Turkish, Full text
Result: 9 hits
Selected: 3 sources
The three selected sources ([7], [9], and [25]) were selected as they provide an overview of the general state of the field, in line with the thesis objective. These sources provide an overview of the current state of artificial intelligence in the field of digital pathology, its potential applications, and its integration into clinical workflows. Articles focusing on a disease subtype or a single case study (e.g., specific hematology or gastroenterology) were excluded.

• Search Strategy: (digital pathology AND biobank) AND (standardization OR “ISO” OR “data management”)
Filters: Review, 2010-2025, English/Turkish, Full text
Result: 9 hits
Selected: 2 sources
These references ([10] and [23]) were chosen since they address the relationship between data management and standardization of digital biobanks, as well as the application of artificial intelligence to these databases.
The articles serve as a resource for why standardization is necessary when managing data, such as clinical data, as well as what AI can accomplish.

• Search Strategy: "digital pathology" AND ("clinical research" OR "translational research") "analysis" "AI"
Filters: 2010-2025, English/Turkish, Full text
Result: 31 hits
Selected: 3 sources
These sources ([10], [20], and [32]) were selected based on use of AI in digital pathology and biobanking related to clinical and translational research. The sources offered an important understanding of AI-driven workflows in digital pathology and biobanking, addressing both technological opportunities and methodological challenges. Other references retrieved in searches were excluded

since they focused primarily on specific study objectives. These search results may refer to digital pathology, but this may not be sufficiently relevant in the context of “clinical research” and the thesis's focus on “biobanks.”

• Search Strategy: "digital pathology" AND ("clinical" OR "advantages")
Filters: Review, 2010-2025, English/Turkish, Full text, Humans species
Result: 281 hits
Selected: 4 sources
The following resources (7, 9, 13, 32) show how digital pathology has developed from technological innovation to clinical practice that has been verified. They were chosen because they focus on the integration of artificial intelligence and image analysis to improve diagnostic accuracy and translational research findings, while also addressing the practical benefits and clinical usability of digital pathology.

Search engine: ScienceDirect
• Search Strategy: "digital pathology” and "biobanking" in human

- Year: 2010-2025
- Title: digital pathology – biobank → Advanced search

Result: 2 hits
Selected: 2 sources
In an advanced search conducted on the ScienceDirect database, publications containing both the terms ‘Digital Pathology’ and ‘Biobanking’ in the title and covering the period 2010-2025 were filtered. The two key studies obtained as a result of this search were selected because they directly addressed the scope of the research. The study by Bonizzi et al. (2021) was included because it represents the transformative role of digital pathology in translational medicine and the beginning of a new era; the study by Wei and Simpson (2014) was included because it focuses on technical infrastructure requirements such as quality assurance and data harmonization in biobanking.

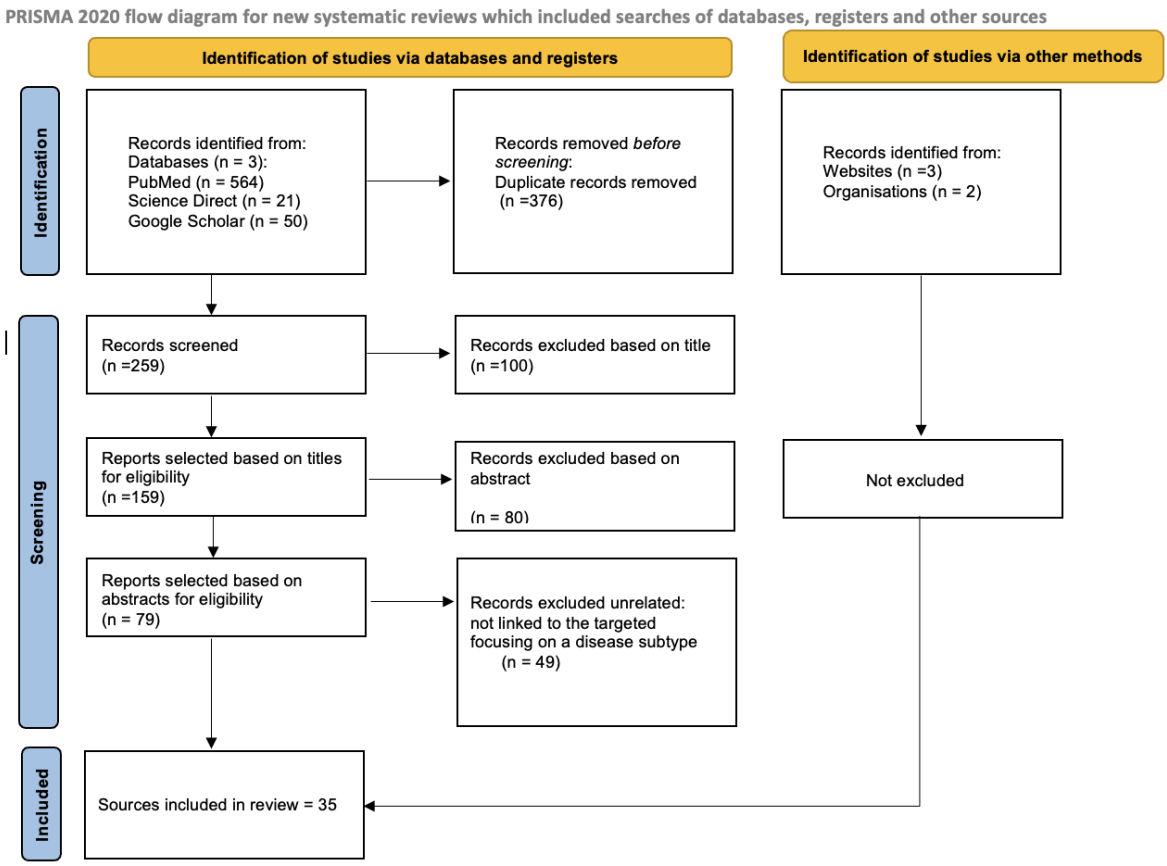


Figure 3. PRISMA flow diagram of the study selection process

As illustrated in the PRISMA flow diagram (Figure 3), different search engines were used to identify relevant articles and publications. The majority of the searches were conducted through PubMed, given its comprehensive coverage of biomedical and clinical research literature. Additional relevant publications identified through keyword searches in other databases were also included when they aligned with the area of the thesis. These duplicates were carefully screened to avoid repetition. Ultimately, studies that were thematically relevant and addressed the core concepts of digital pathology, biobanking, artificial intelligence, or clinical research were included in the analysis.

A total of 35 sources were analyzed. The selected publications were classified under thematic headings using content analysis methods. These themes are as follows:

1. Technical developments in digital pathology
2. Integration of artificial intelligence

3. Clinical research application areas
4. Ethical, legal and governance aspects

Table 2. Overview of all 35 publications selected for this thesis

No	Publication	Year	Category	Main Topic / Contribution	Reason for Inclusion
1	Jahn et al.	2020	Digital Pathology – Advantages	Advantages, limitations, emerging perspectives	Direct relevance to advantages section
2	Talu et al.	2020	Biobanking	Biobanking fundamentals, tissues	Supports DP–biobank link
3	Wei & Simpson	2014	Digital Biobanking	DP & image analysis improving biobank QA	Strong DP–biobank interaction
4	Moscalu et al.	2023	AI–DP	Predictive modeling, computational pathology	Relevant to AI integration
5	Yu et al.	2024	Ethics	AI ethics in medical research	Supports ethics section
6	Hijazi et al.	2024	DP in Clinical Practice	Improved workflow, precision	Clinical practice relevance
7	Viswanathan et al.	2022	AI–Lung Pathology	AI for lung DP	Specific AI application
8	Pell et al.	2019	Clinical Trials	DP in clinical trials	Supports clinical workflow
9	Colling et al.	2019	AI Roadmap	Roadmap to DP-AI adoption	Methodological relevance
10	Frascarelli et al.	2023	Digital Biobanking	AI in biobanking	DP–AI–biobank triad
11	Vaught & Lockhart	2012	Biobanking	Best practices	Background biobank theory
12	Zatloukal & Hainaut	2010	Biobanking	Tissue biobanking in drug development	Fundamental reference
13	Hamilton et al.	2014	Biomarker Research	DP for biomarker analysis	Tissue-level focus
14	Alkhatib & Gaede	2024	Data Management	Biobank data challenges	Modern biobank data issues

15	Cornell Biobank	—	Biobank Info	Structural background	General understanding
16	CABI Report	2024	Biobank Policy	UK microbiome biobank	Different type of biobank
17	Clinical Trials Review	—	Clinical Trials	Understanding CT framework	Supports DP-in-clinical context
18	FDA Step 3	2019	Regulatory	Clinical Research regulation	Regulatory foundation
19	FDA Step 2	2019	Regulatory	Preclinical Research	Regulatory background
20	Bonizzi et al.	2021	Biobanking	Biobanking within DP era	DP-era biobank structure
21	Borowsky et al.	2022	Slide-Free Imaging	FIBI validation	Alternative imaging technology
22	Hanna & Ardon	2023	DP Systems	Quality & patient care	Clinical performance relevance
23	Brancato et al.	2024	Digital Biobanks	Imaging + genomic integration	Precision medicine
24	Shafi & Parwani	2023	AI in DP	Overview of AI	Supports AI chapter
25	Bera et al.	2019	Precision Oncology	AI + DP in oncology	High-impact AI work
26	Emir	2013	Ethics	Biobank ethics	Turkish context
27	Biobank Ethics Guide	—	Ethics	Legal and ethical guidelines	Regulatory context
28	Bruns & Winkler	2024	Consent	Dynamic consent	Patient rights relevance
29	Sorell et al.	2021	Ethics in DP	Computational pathology ethics	Ethics chapter strength
30	Verdicchio & Perin	2022	Human–AI Interaction	AI responsibility	Human–AI risk discussion
31	Huang et al.	2022	Bias	Racial bias in ML models	DP-AI fairness issue
32	Baxi et al.	2022	Translational Medicine	DP & AI in translation	Strong methodological paper
33	Munari et al.	2024	Lab Technology	New automation technologies	DP in lab innovation

34	ISO 15189 Guide	—	Accreditation	DP for quality accreditation	Quality chapter relevance
35	FDA WSI Approval	2024	Regulation	First WSI marketing approval	Regulatory cornerstone

The table above summarizes an overview of the 35 publications selected in this thesis, including their publication year, topic category, and how they contribute.

5 RESULTS

As a result of the literature review conducted within the context of this thesis, digital pathology is bringing about significant developments in the field of biobanking, and more are planned. It is seen to be bringing about a significant transformation in clinical research and diagnostic processes. Digital systems must more systematically comply with regulatory authority requirements (FDA, CE-IVD) and international quality standards (e.g., ISO 15189, ISO 20387:2018) in order for this transition to take place in a sustainable and dependable manner. (23,34) The use of these approved systems enhances the validity of scientific results and provides a safe framework in terms of ethics and regulation. (8,35)

Whole slide imaging (WSI) technology enables the comprehensive analysis of FFPE tissues and reduces data loss. The digitization of slides has led to significant gains in remote access, data sharing, and quality control processes. Innovative approaches such as slide-free imaging have increased the level of automation in pathology laboratories. (21) The reliable use of Whole Slide Imaging (WSI) technology in clinical diagnostic processes depends not only on its technical capabilities but also on validation, quality control, and data security practices. (22)

Digital pathology and biobanking play a critical role in translational medicine in terms of biomarker discovery and targeted therapy development. The combination of samples stored in biobanks with digital image analysis has accelerated translational research. (20)

In the literature review conducted as part of the thesis study, the most discussed ethical issues in the studies were broad/dynamic consent, data security, transparency in artificial intelligence, and commercialization. The concept of “dynamic consent” in the literature stands out as a new model proposed for more effective protection of participant rights. Regulations such as the GDPR require digital pathology systems to operate in accordance with the principles of data minimization and transparency. (5,29)

Artificial intelligence is increasingly being used in areas such as biomarker analysis, diagnosis, and classification, demonstrating one of the most remarkable aspects of digital pathology. In complex disease groups such as lung pathology, Artificial Intelligence (AI) tools can not only diagnose from tissue images in complex disease groups like lung pathology, but also carry out crucial tasks like predicting molecular subgroups and treatment response. (7) However, as the study made clear, high-resolution, standardized, accurately annotated data is just as important to the success of AI systems as their technical capacities. Therefore, to truly capitalize on the benefits offered by digital pathology, strengthening the infrastructure in line with both quality standards and data management principles has become essential.

This section presents the results of a systematic review conducted on 35 selected sources. The reviewed literature is primarily grouped into three main areas: Artificial Intelligence and Technical Integration (AI Usage & Tech), Ethical and Legal Issues (ELSI), and Biobanking & Data Management.

The distribution of studies by country and an overview of the main topics they focus on are summarized in Table 3.

Table 3. Summary of selected studies categorized by geographic origin and thematic focus

Reference (First Author)	Ref No	Country	AI Usage & Technical Integration	ELSI	Biobanking & Data Standards
Jahn et al. (2020)	**1**	Austria	✓	-	-
Talu et al. (2020)	**2**	Türkiye	-	✓	✓
Wei & Simpson (2014)	**3**	USA	✓	-	✓
Moscalu et al. (2023)	**4**	Romania	✓	-	-
Yu et al. (2024)	**5**	Korea	✓	✓	✓
Hijazi et al. (2024)	**6**	Global	✓	-	-
Viswanathan et al. (2022)	**7**	USA	✓	-	-
Pell et al. (2019)	**8**	UK	✓	-	-
Colling et al. (2019)	**9**	UK	✓	-	-
Frascarelli et al. (2023)	**10**	Italy	✓	✓	✓

Vaught & Lockhart (2012)	**11**	USA	-	✓	✓
Zatloukal & Hainaut (2010)	**12**	Austria/France	-	-	✓
Hamilton et al. (2014)	**13**	UK	✓	-	-
Alkhatib & Gaede (2024)	**14**	Germany	✓	✓	✓
Cornell Vet. Biobank	**15**	USA	-	-	-
UK Microbiome Report	**16**	UK	-	-	-
Kandi (2023)	**17**	India	-	-	-
FDA (Clinical Research)	**18**	USA	-	-	-
FDA (Preclinical)	**19**	USA	-	-	-
Bonizzi et al. (2021)	**20**	Italy	✓	-	✓
Borowsky et al. (2022)	**21**	USA	✓	-	-
Hanna & Ardon (2023)	**22**	USA	✓	-	✓
Brancato et al. (2024)	**23**	Italy	✓	✓	✓

Shafi & Parwani (2023)	**24**	USA	✓	-	-
Bera et al. (2019)	**25**	USA	✓	-	-
Emir (2013)	**26**	Türkiye	-	✓	✓
Biyobankalar Kılavuzu	**27**	Türkiye	-	✓	✓
Bruns & Winkler (2024)	**28**	Germany	-	✓	-
Sorell et al. (2021)	**29**	UK	-	✓	-
Verdicchio & Perin (2022)	**30**	Italy/Germany/Chile	✓	✓	-
Huang et al. (2022)	**31**	USA	✓	✓	-
Baxi et al. (2022)	**32**	USA	✓	-	-
Munari et al. (2024)	**33**	Italy	✓	-	-
ISO 15189 Guide	**34**	Intl.	-	-	✓
FDA (WSI Approval)	**35**	USA	✓	-	-

Table 3 presents a comprehensive review of 35 sources categorizing the current landscape of digital pathology and biobanking. The literature is analyzed based on

three critical dimensions: AI Usage & Technical Integration, Ethical, Legal, and Social Implications (ELSI), and Biobanking & Data Standards.
Geographically, the research landscape is predominantly driven by institutions in the United States and Europe (especially Italy, the UK, and Germany), which together contribute most technical validation studies. However, the inclusion of studies from Türkiye (2, 26, 27) and Korea (5) highlights the growing global effort to harmonize local regulatory frameworks with international biobanking standards.
A cross-sectional analysis of the table reveals three significant trends:

- Predominance of Technical Validation: AI Usage and Technical Integration is the most represented category, appearing in 22 of 35 sources (approximately 63%).

  This indicates that the field is currently focused on the "proof of concept" phase, prioritizing the validation of algorithms and Whole Slide Imaging (WSI) technologies (6, 7, 35) rather than addressing downstream integration challenges.

- Separation of Ethical and Technical Topics: While ethical and legal considerations are discussed in 12 sources, they often appear in studies dedicated solely to governance. Interestingly, while many technical AI studies acknowledge ethical concerns (e.g., privacy risks), they frequently lack integration with specific legal frameworks or established biobanking standards within their methodologies. This suggests a lack of integration in the literature, where technical developers and ethicists appear to be working separately rather than in collaboration.

- Emergence of Holistic Models: A small but critical cluster of studies, specifically Yu et al. (5), Frascarelli et al. (10), Alkhatib & Gaede (14), and Brancato et al. (23), bridges all three categories. These studies are particularly significant for this thesis as they demonstrate that successful digital pathology implementation requires the simultaneous alignment of AI capability, ethical compliance, and biobanking data standards.

In line with this general distribution, the identified sub-topics (sub-results) are detailed below.

5.1 Sub-result dealing with Artificial Intelligence and Technical Integration

Table 4. Sub-result: Artificial Intelligence and Technical Integration

Reference / Ref No	AI& TI	Quantification	Advantages	Disadvantages	Technique
Jahn et al. (2020) / 1	Yes	-	-Objectivity - Reproducibility -Remote access	-High cost of scanners -Storage capacity limits	WSI / Digital Pathology
Wei & Simpson (2014) / 3	Yes	Quality assurance	-Improves biospecimen annotation quality	-	Image Analysis
Moscalu et al. (2023) / 4	Yes	Predictive modeling	- Identification of predictive markers - Faster workflows	-GDPR automated decision limits -Black-box ML	DP WSI AI
Yu et al. (2024) / 5	Yes	-	-Clinical decision support	-"Black box" nature -Algorithmic bias -Data privacy/security -Accountability issues	AI-supported decision-making systems

Hijazi et al. (2024) / 6	Yes	Counting cell	-Detects smallest abnormalities -High resolution -Reduces human error	-Cost -Regulatory approvals -Data quality -Multi step validation	WSI AI
Viswanathan et al. (2022) / 7	Yes	Morphology & biomarker quantification, pathomics	-Diagnosis in complex cases - Workflow support	-Storage -Cost - "Black box" nature	DP/WSI AI
Pell et al. (2019) / 8	Yes	-	-Utility in clinical trials -Logistic -Flexible -Distance learning	- Data governance and research approval - Safely incorporate developments	-DP -Image Analysis
Colling et al. (2019) / 9	Yes	-	-Reproducibility -Time	-Financing scanners and software -Long-term data storage	AI
Frascarelli et al. (2023) / 10	Yes	AI-based quantitative analysis	-Speed -Accuracy -Remote capabilities	-Potential inaccuracies -Data privacy concerns	-AI -DP -LIMS

Hamilton et al. (2014) /13	Yes	Tissue biomarker research; Diagnostic marker development	-Pathology outsourcing -Remote access -Productivity -Efficiency	-Algorithm configuration -Risk in inexperienced hands -Pre-analytical variability -Storage burden	-Image analysis
Alkhatib & Gaede (2024) / 14	Yes	-	- Data integrity	-Challenges regarding privacy -Consent -Ownership -GDPR/HIPAA compliance	Advanced Technologies; AI,ML
Bonizzi et al. (2021) / 20	Yes	-	-Teleconsultation-Resource usage	-Data gaining -Storage -Practice	-DP -AI
Borowsky et al. (2022) / 21	Yes	-	-Improved speed -Reduced cost -Better conservation of tissue	-	-Slide-Free Imaging (FIBI)
Hanna & Ardon (2023) / 22	Yes	-Tumor detection -Subtyping,	-Higher interobserver agreement	-Specialized equipment and expertise	-ML -AI

		-Mitosis quantification	and accuracy -Remotely collaboration reduce the time and cost		
Brancato et al. (2024) / 23	Yes	Radiomic & Pathomic features (Numerical descriptors)	Reproducibility of features; Supports precision medicine models	-Data heterogeneity -Lack of standardization -Privacy concerns	-MIABIS -DICOM -FASTQ
Shafi & Parwani (2023) / 24	Yes	Quantitative Histomorphometry; Cell quantification; Gleason grading	Standardizes scoring (reduces variability); Diagnostic accuracy; Workflow efficiency	-Regulation/ approval -Computation system and data storage	Diagnostic Pathology AI (WSI/ML/DL)
Bera et al. (2019) / 25	Yes	Sub-visual morphometric phenotypes	-Diagnostic accuracy -Biomarker development -Subvisual feature mining	-Need for well-curated validation datasets -Regulatory ethics -Interpretability limits	-ML -DL

Verdicchio & Perin (2022) / 30	Yes	-	Clinical Decision Support (Supports rather than replaces)	-Black-box opacity -Unclear accountability -Risk assessment limits -Moral agency gap -Danger of overreliance	AI systems; DL, SVM
Huang et al. (2022) / 31	Yes	-	Potential for improved fairness & safer ML models	-Racial bias -Dataset imbalance - Poor generalizability	Clinical ML
Baxi et al. (2022) / 32	Yes	cell scoring, PD-L1, feature quantification	-FDA-approved primary diagnosis - Long-term accessibility - Translational medicine support	-High scanner & infrastructure costs -Storage requirements	-WSI -AI -ML
Munari et al. (2024) / 33	Yes	-	-Automation of laboratory workflow -Digital archiving support	-Cost -Training needs -Privacy - Standardization -Validation	DP + automation integration

			-Discover unique patterns and biomarkers		

Bringing Artificial Intelligence (AI) and Machine Learning (ML) into digital pathology has greatly improved diagnostic tools and biobanking processes. The literature shows that AI is mainly used for image visualization, advanced measurements, and decision support. Table 4 gives an overview of technical uses, specific measurement tasks, and the main benefits and drawbacks found in the studies. One key finding is the move from simply observing to actually measuring results. Table 4 shows that several studies found AI can handle specific measurement tasks and help reduce differences between observers. For instance, Hijazi et al. (6) show that AI is effective at "counting cells" and spotting small abnormalities in high detail. Viswanathan et al. (7) describe how AI helps with "morphology and biomarker quantification" (pathomics). More advanced uses, such as "predictive modeling" Moscalu et al. (4), help identify predictive markers and speed up work compared to older methods.

The studies reviewed highlight important practical benefits. Jahn et al. (1) and Yu et al. (5) found that AI-supported systems produce more objective results, are more reproducible, and provide clinical decision support. In biobanking and research, Wei & Simpson (3) note that image analysis improves "biospecimen annotation quality," which is key for Quality Assurance (QA). Pell et al. (8) also point out that these systems can be adapted for "clinical trials" and distance learning.

Even with these benefits, using these technologies widely still faces significant challenges. Technical and financial issues, like the "high cost of scanners" and "storage capacity limits," are often significant barriers (Jahn et al., (1); Viswanathan et al., (7)). There are also important ethical and regulatory concerns. The "black box" nature of AI systems raises questions about transparency and accountability (Yu et al., (5); Verdicchio & Perin, (30), and automated decision-making raises specific issues regarding GDPR compliance and data management.

5.2 Sub-result dealing with ELSI

Table 5. Sub-result dealing with ELSI

Reference / Ref No	Ethics	IC Model	Data Privacy	AI Transparency
Talu et al. (2020) / 2	✓	Explained IC types	Anonymization	-
Yu et al. (2024) / 5	✓	-	-De-identifying encrypting	(Black box)
Frascarelli et al. (2023) / 10	✓	-	-	Lack of transparency
Vaught & Lockhart (2012) / 11	✓	Broad Specific	Develop policies to deal with possible unauthorized disclosures	-
Alkhatib & Gaede (2024) / 14	✓	Dynamic	-Anonymization -Encryption -Prevent unauthorized access	-
Brancato et al. (2024) / 23	✓	-	-GDPR -FAIR	-Black box -Lacking interpretability
Emir (2013) / 26	✓	Broad consent	WHO; anonymization	-

Bruns & Winkler (2024) / 28	✓	Dynamic over broad consent	-	-
Sorell et al. (2021) / 29	✓	Broad consent	-GDPR -European Union -UK data protection law	Opacity & accountability
Verdicchio & Perin (2022) / 30	✓	-	-GDPR	Black box

The review of references in Table 5 reveals that all ten publications report ethical considerations; however, the depth of discussion varies between studies. For informed consent, the table indicates multiple models. Broad consent is mentioned in Vaught & Lockhart (11), Emir (26), and Sorell et al. (29), while dynamic consent has support from Alkhatib & Gaede (14) and Bruns & Winkler (28). Talu et al. (2) also presents “explained IC types,” which further reflects the variations in approaches to documenting consent.

Data privacy is another issue taken up by several sources. Privacy measures such as anonymization, encryption, and preventing unauthorized access are noted in Talu et al. (2), Alkhatib & Gaede (14), Emir (26), and Yu et al. (5). Regulatory frameworks including GDPR, FAIR, and broader European or UK data protection laws appear in Brancato et al. (23) and Sorell et al. (29); Vaught & Lockhart (11) highlight the need for policies to prevent unauthorized disclosures.

Finally, AI transparency is another recurring concern. Several publications note risks from opaque or "black box" AI systems, including Yu et al. (5), Brancato et al. (23), and Verdicchio and Perin (30). Frascarelli et al. (10), as well as Sorell et al. (29), further emphasize transparency-related issues such as lack of interpretability, lack of clarity, opacity, and accountability.

5.3 Sub-result dealing with Standardization and Data Management

Table 6. Sub-result dealing with Standardization and Data Management

Reference / Ref No	Standardization	Data Management
Talu et al. (2020) / 2	ISO 9001, ISO 17025 and ISO 15189	Collection, Recording, Storage, Security
Wei & Simpson (2014) / 3	QA Harmonization; Biospecimen annotation quality	-
Yu et al. (2024) / 5	-	-Collection, Storage, Security, Anonymization, Sharing and re-use -GDPR and HIPAA
Frascarelli et al. (2023) / 10	IARC ISO ISBER	LIMS Collection, Usage, Quality Multi-modal Dataset Integration
Vaught & Lockhart (2012) / 11	SOP Best Practices (NCI and ISBER)	Collection, Processing, Storage, Quality, Ethical and Regulatory
Zatloukal & Hainaut (2010) / 12	-	-Evidence-based protocols -Common data formats
Alkhatib & Gaede (2024) / 14	SOP MIABIS FAIR	GDPR, HIPAA

Bonizzi et al. (2021) / 20	ISO 15189 and ISO 17025 SOP	LIMS Data must be safe, accessible, and traceable
Hanna & Ardon (2023) / 22	Validation; Quality Control (QC	LIS
Brancato et al. (2024) / 23	ISO 20387:2018 DICOM MIABIS SOP	Data Catalog JavaScript Object Notation (JSON); human-readable data structure
Emir (2013) / 26	European Union biobank standards	Legal data handling

Review of the studies listed in Table 6 shows that both standardization and data management practices are discussed at different levels of detail across the selected references. Standards related to biobanking and digital pathology are frequently cited, highlighting the need for harmonized procedures and strong quality frameworks. Several publications highlight the significance of internationally recognized standards, including ISO 9001, ISO 17025, ISO 15189, and ISO 20387:2018, as reported by Talu et al. (2), Bonizzi et al. (20), and Brancato et al. (23). Furthermore, domain-specific frameworks such as SOPs, ISBER guidelines, NCI best practices, IARC standards, DICOM, MIABIS, and FAIR principles are referenced in multiple studies, illustrating the range of standardization approaches in digital pathology and biobanking workflows.

Table 6 also demonstrates that data management is addressed through both operational processes and information systems that support sample handling and digital data workflows. Several references emphasize core biobank operations, including collection, recording, processing, storage, security, and quality control, as noted in Talu et al. (2), Vaught & Lockhart (11), and Hanna & Ardon (22). More advanced data infrastructures are identified in studies such as Frascarelli et al. (10) and Bonizzi et al. (20), which reference systems such as LIMS, while Hanna

& Ardon (22) discuss the role of LIS. Data management considerations also include data cataloging and the use of human-readable formats such as JSON, which facilitate interoperability between imaging and biobank environments, as observed in Brancato et al. (23). Regulatory considerations, including GDPR, HIPAA, and legal data handling, are addressed in studies such as Yu et al. (5), Alkhatib & Gaede (14), and Emir (26), highlighting the critical importance of compliance in integrated digital-biobank systems.

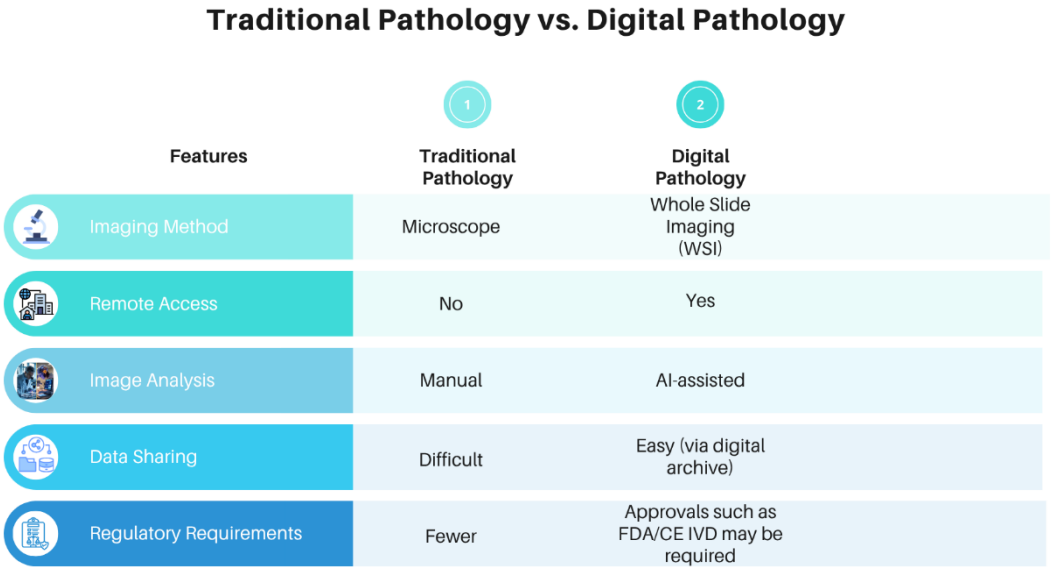
In summary, Table 6 shows that while standardization frameworks are widely cited in the literature, data management practices vary from basic operational procedures to complex multimodal integration systems. This variability reflects different stages of digital pathology and biobanking maturity across the reviewed references.

6 DISCUSSION

The literature review conducted in this thesis has revealed that digital pathology is not only a technological innovation in biobanking and clinical research, but also a fundamentally changing process. Compared to traditional methods, digital pathology systems offer many advantages, such as higher-resolution imaging, remote access, and support for analysis with artificial intelligence. However, for these advantages to be fully effective, the systems must be installed and operated in accordance with specific quality standards and data management principles. The literature further indicates that digital pathology is shifting biobanking from physical repositories to dynamic digital data hubs. While traditional biobanking focused on preserving tissue integrity, Whole Slide Imaging (WSI) now allows biobanks to generate, store, and share high-resolution morphological data without repeated use of physical samples. This expands the functional and scientific value of biobank collections.

The advantages of digital pathology over traditional methods in biobanking demonstrate why this transformation is necessary. The table below summarizes the key aspects of these differences (Table 7).

Table 7. Comparison of traditional pathology and digital pathology



While technologies such as Whole Slide Imaging (WSI) have been approved by institutions such as the FDA and CE-IVD, compliance with international standards such as ISO 15189 (for clinical diagnostic laboratories) and ISO 20387 (for biobanks) is crucial for safe and sustainable long-term use (23,34). Particularly in multi-center studies, variations in image formats or annotation methods can undermine the reliability of the results. Consequently, using common data formats such as DICOM and ensuring data interoperability are essential.

The widespread use of digital systems facilitates diagnostic accuracy, data sharing, and artificial intelligence integration, but also brings new challenges such as costs and regulations. This situation requires an evaluation of the advantages and challenges of both traditional and digital pathology (Table 7).

Artificial intelligence stands out as one of the most striking aspects of digital pathology. Viswanathan et al.'s (7) study showed that AI not only performs image analysis but can also predict molecular subgroups by cancer type and perform advanced analyses such as predicting treatment response. (7) However, for such systems to function correctly, they require not only powerful algorithms but also high-quality, well-annotated, and standardized datasets. The reliability of the

results produced by these systems becomes significantly questionable when working with low-quality data.

Ethical and legal factors support developments in this field by increasing trust in digital systems, but at the same time, they can restrict certain applications due to sensitive issues such as data privacy. Data protection laws such as GDPR and HIPAA establish clear rules on how patient data should be stored and under what circumstances it can be reused. While participant-driven consent models such as dynamic consent may seem like a solution in theory, practical implementation differences can complicate this process. Furthermore, the fact that AI's decision-making mechanisms are not always transparent (the "black box" structure) raises the question of who is responsible in the event of a potential error. (30)

6.1 Accuracy Outcomes Linked to AI and Technical Integration in Digital Pathology

The result of Table 4 consistently highlights the capacity of AI to enhance diagnostic precision, particularly in tasks such as cell counting and mitosis quantification. AI-supported image analysis has been shown to reduce interobserver variability, provide more objective quantification of histological features, and support the detection of subtle morphological patterns that may be overlooked during conventional microscopy. Improvements in accuracy are directly associated with advancements in technical integration, such as high-resolution whole-slide imaging, standardized digital formats, and interoperable data lines that maintain image fidelity during acquisition, storage, and analysis. (36) When these technological components are aligned, AI systems can deliver reproducible outputs that strengthen both clinical interpretation and research reliability.

Although the performance of artificial intelligence is comparable to that of pathologists, analyses show that pathologists still perform better than AI. It is thought that AI is not as sensitive and predictive as pathologists. Consequently, it is emphasized that AI models can be an essential tool in environments where pathologists with sufficient expertise and skills are not available, supporting pathologists, improving diagnostic skills, and enhancing diagnostic capabilities among pathologists with different areas of expertise. Integrating AI into a process

supervised and guided by pathologists will be vital for diagnostic performance and assessment skills. (37)

Some studies have evaluated the usage rates of these developing scanners. 85% of those interested indicated that they were highly or very likely to use them for diagnostic purposes, while 92.5% reported a high likelihood of using them for consultations. (38)

6.2 Ethical, Legal, and Regulatory Implications

This thesis's ethical and legal findings indicate that the transition to digital pathology affects not only technology adoption but also how biobanks govern data, manage consent, and maintain public trust and presents governance difficulties that are equally substantial as the technological ones. Numerous publications highlight that informed consent lies at the center of these challenges, yet the literature offers differing perspectives on how consent models should evolve. For example, Vaught and Lockhart (11) and Emir (26) both describe broad consent as a practical model for long-term biobank use, yet more recent authors argue that its limitations become evident once digital images and AI workflows are introduced. Bruns and Winkler (28) highlight that participants increasingly expect ongoing control over how their samples and data are used, which strengthens the case for dynamic consent. However, these models require considerable technical and administrative support, meaning they may not be feasible for all institutions.
Privacy concerns are equally prominent. Sorell et al. (29) and Brancato et al. (23) point out that whole-slide images can fall under GDPR, even when pseudonymized, because they may contain identifiable information when combined with other datasets. This aligns with observations from Yu et al. (5) and Heseltine-Carpet al. (44), who note that GDPR's emphasis on data minimization conflicts with AI's constant need for large, diverse, and reusable datasets. These tensions create practical challenges for biobanks that aim to support AI research while remaining fully compliant with regulatory standards.
Another important topic in the literature is accountability in AI-supported diagnostics. Verdicchio and Perin (30) question how responsibility should be assigned when algorithmic outputs are not fully interpretable, and similar concerns are raised by Huang et al. (31) regarding dataset bias.

Overall, these publications collectively underscore that ethical and regulatory considerations must develop in parallel with technical innovation. Digital pathology offers clear benefits, but its long-term success depends on transparent governance, robust data protection practices, and consent models that reflect the realities of digital and AI-driven research.

6.3 Standardization Challenges

Standardization consistently emerges as a significant limitation in the literature. While digital pathology has the potential to enable interoperability, its implementation remains fragmented. Frascarelli et al. (10), Brancato et al. (23), and Vaught & Lockhart (11) emphasize the importance of ISO standards, standard operating procedures (SOPs), and uniform metadata models; however, global compliance with these frameworks is inconsistent.
A key barrier is standardization: different labs use different protocols, different scanners, different slide-prep, and staining intensity. Without systematic standardization (or robust calibration/augmentation methods), AI tools risk "breaking" when transferred to a new site. (39, 40)

There are also considerations around data privacy, interoperability (e.g., using standards such as DICOM and WSI), validation across populations/institutions, and ensuring clinicians trust and verify AI outputs. (40,41)

The transition to standardized frameworks such as MIABIS, FAIR principles, and DICOM in pathology represents significant progress; however, implementation remains inconsistent. The literature states that standardization is primarily a matter of governance and coordination rather than a purely technical concern, necessitating the following:

1. Establishing cross-institutional agreements,
2. Applying regulatory pressure, and
3. Ongoing training of personnel.

Without addressing these issues, digital pathology systems may result in a lack of technologically advanced interoperability. Thereby undermining their translational potential.

6.4 The Evolution into "Digital Biobanking"

Digital pathology enables biobanks to offer "in silico" samples alongside physical ones. This capability solves a major limitation in traditional biobanking: the exhaustion of finite tissue samples. By digitizing a slide once, biobanks can facilitate unlimited remote analyses for multi-center studies without ever touching the original paraffin block again. Furthermore, linking this imaging data with genomic and clinical metadata (as emphasized in the MIABIS and ISO 20387 standards) creates "multi-modal" datasets. (42) These enriched datasets significantly increase the scientific and commercial value of biobank cohorts for pharmaceutical research and biomarker discovery.

Digital pathology represents a significant technological advancement. It shifts biobanking from passive storage to active utilization. This change redefines biobanking as a dynamic data infrastructure that continuously supports clinical research. The adoption of standardized metadata and high-quality whole slide imaging (WSI) files facilitates the transition from physical glass slides to digital assets, thereby enhancing the analytical potential of archived tissue collections and enabling studies involving artificial intelligence. As biobanking evolves, it assumes increased responsibility for pre-analytical quality control. It also promotes collaboration in large-scale translational research through multi-center coordination, ultimately leading to more reliable research outcomes.

In summary, integrating digital pathology into biobanking constitutes a substantial transformation. It modernizes operational processes, strengthens contributions to clinical research, and establishes biobanks as central participants in the advancement of medical research.

6.5 The Economic Reality of Digital Storage

The scientific advantages of digital pathology are evident, although the economic implications of its implementation in a biobank context are frequently undervalued. Jahn et al. (1) cited "high scanner costs" as a limitation.

Biobanks face significant economic pressures because data must be preserved for decades and often lack the dedicated budgets of clinical institutions. Long-term storage of digital files, genomic data, and clinical metadata increases storage requirements. Vendor-independent repositories (VNAs) and cloud-based systems help reduce some of this burden. Federated VNAs can be cheaper and faster to install due to their lower hardware specifications, but they may have more difficulty connecting to multiple image sources. (33)

With multiple duplicate studies in DP archives, high-resolution WSI files can range from hundreds of megabytes to several gigabytes per slide, generating terabytes of data annually for large pathology departments. The results already highlight these concerns, particularly the cost of scanners, infrastructure, and long-term archiving. Although the initial investment in scanners and storage is high, it yields a sustainable return on investment by preserving the physical integrity of biospecimens and enabling the reuse of digital data for future AI training sets. (10,43)

Thus, the economic realities of digital storage directly affect biobanks' capacity to preserve tissue integrity, provide high-quality digital assets, and participate competitively in international research networks.

6.6 Telepathology and Remote Collaboration

The results confirm that Whole Slide Imaging (WSI) effectively breaks down the physical barriers of traditional microscopy. While traditional pathology requires the physical shipment of fragile glass slides—risking breakage and delay—digital pathology enables instant "teleconsultation". The reviews by Bonizzi et al. (20) and Hanna & Ardon (22) demonstrate that this is not merely a logistical improvement but a quality assurance mechanism.

Digital pathology enables rapid second opinions and remote collaboration, thereby expanding access to sub-specialist expertise. This ensures that complex biobank samples or rare clinical cases can be reviewed by experts irrespective of geographic location.

However, to fully realize these benefits, the infrastructure challenges identified in the economic analysis, such as the need for high-speed bandwidth and secure firewalls, must be addressed to prevent latency from impeding the diagnostic process.

For biobanking, telepathology supports:

- Distributed review of rare specimens,
- Harmonization of tissue quality grading,
- Multi-center annotation for AI training, and
- International collaborations that depend on consistent digital access.

However, telepathology also introduces challenges related to bandwidth, image compression, latency, and cybersecurity. (14,23) These issues may disproportionately affect institutions in low-resource settings, widening global inequality in research capabilities.

Nonetheless, telepathology remains one of the most mature and impactful applications of digital pathology, with strong evidence supporting its continued expansion.

Telepathology strengthens the operational resilience of biobanks and enhances the long-term research value of specimen collections by enabling remote evaluation of tissue quality, streamlining expert consultation, and reducing the need for repeated physical slide handling.

6.7 Challenges in the Transformation to Digital Pathology

Despite its advantages, the transition to digital pathology is complex and multidimensional. The reviewed studies and additional literature point to several key barriers:

- Human and organizational barriers
- Ethical and legal barriers
- Financial and sustainability barriers
- Technical barriers
- Validation and regulatory barriers

While the transition to digital pathology is often characterized as a technical upgrade, it also represents a significant cultural and operational transformation. As noted in the results (Munari et al. [33]), automation requires new training. Resistance to this transition often stems from the “black box” nature of AI systems and concerns about professional displacement.
Operational challenges are also significant. In contrast to radiology, where imaging is performed directly on the patient, pathology relies on a series of pre-analytic steps, including fixation, embedding, sectioning, and staining. Deficiencies at any of these stages, including tissue folds, uneven staining, or sectioning artifacts, can compromise the quality of the resulting digital image. (13) In biobanking, this creates a quality control that must shift upstream to focus on physical slide preparation, not just digital acquisition. Flawed glass slides produce digital records that are unsuitable for downstream uses such as AI training, algorithm validation, or multi-center data harmonization.

6.8 Future Perspective

The findings of this thesis indicate that digital pathology integration into biobanking is at an early stage and requires improvement in several areas before its full potential can be realized. Future work should focus on developing large, high-quality, demographically diverse datasets to overcome current limitations in AI training, such as model bias and poor generalizability. Strengthening international

standardization efforts, particularly in metadata structure, image formats, and biospecimen annotation, will be necessary for enabling seamless data exchange between institutions. Additionally, long-term sustainability should be considered through cost-effective storage solutions and harmonized digital archiving systems applicable to biobank environments. Ethical and legal frameworks will also need adjustments to accommodate dynamic consent models, along with transparent AI governance and secure data reuse. Finally, closer collaboration among biobanks, pathology units, data scientists, and regulators is key for transforming today’s experimental digital workflows into routinely implemented interoperable infrastructure supporting multicenter clinical research and precision medicine.

7 CONCLUSION

Digital pathology should be viewed not only as a technology investment but also as a comprehensive system transformation. It offers a revolutionary approach to biobanking by converting physical glass archives into a sustainable digital data infrastructure. This transformation requires addressing the "black box" accountability concerns in AI, ensuring technical interoperability beyond just file formats, and planning for the long-term economic burden of digital storage. Human resources, institutional training processes, ethical governance structures, and overall organizational readiness for this transformation will be just as decisive as technology itself. If only by balancing these factors, biobanks can fully realize the promise of digital pathology.

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