

## Histopathological Imaging and Artificial Intelligence for Cancer Diagnosis and Gleason Grading: A Brief Review of Prostate Cancer

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### ABSTRACT

**Objective:** Prostate cancer, one of the most common cancers affecting men's health worldwide, ranks second among cancer-related deaths. Therefore, it represents a critical health issue, and early diagnosis is crucial. Several imaging and analytical methods are used to diagnose this condition.

**Materials and Methods:** This study focuses on research conducted between 2021 and 2025 that analyzes, diagnoses, and grades prostate cancer based on histopathological images using machine learning and deep learning algorithms. In this context, the reviewed studies also include an analysis of findings related to preprocessing and feature extraction methods that may aid in prostate cancer detection, as well as the classifiers used.

**Results:** According to the findings of the reviewed studies, artificial intelligence-supported prostate cancer detection systems demonstrate high clinical performance and significantly improve the diagnostic accuracy of pathologists by enabling rapid diagnosis. The presented research findings indicate a need for comprehensive studies focusing on prostate cancer using histopathological images.

**Conclusion:** The integration of artificial intelligence is transforming prostate cancer pathology from a traditional and subjective process into a data-driven and standardized framework. This systematic analysis of histopathological images will make significant contributions to future prostate cancer research, help achieve more reliable results in clinical decision-making processes, and lay the groundwork for personalized medicine.

**Keywords:** Deep learning, Gleason grading, histopathological imaging, machine learning, prostate cancer.



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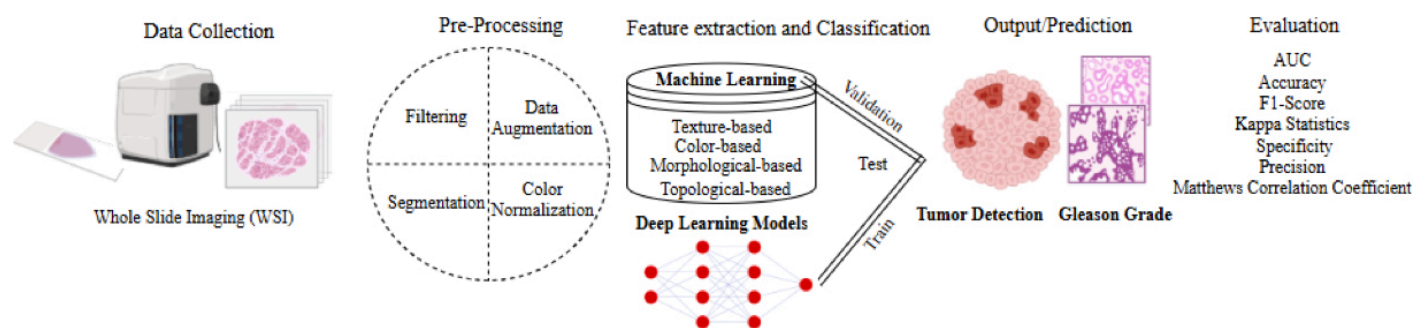
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### INTRODUCTION

Prostate cancer (PCa), one of the most common cancers affecting men's health worldwide, is among the most frequently diagnosed malignant tumors and represents a critical health issue, ranking second among causes of cancer-related death. It shares many characteristics with other cancer types in terms of diagnostic and staging processes.<sup>1–3</sup> Recently published data clearly demonstrate



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**Figure 1.** Artificial intelligence-based analysis of histopathological images.

the substantial burden of morbidity and mortality associated with this disease worldwide.<sup>3–5</sup> The management of this disease, which poses a serious health threat, particularly to the elderly population, relies on accurate risk classification and the determination of appropriate treatment protocols based on precise pathological diagnosis and Gleason grading.<sup>5,6</sup> Various imaging methods, including ultrasound, magnetic resonance imaging (MRI), positron emission tomography, and computed tomography (CT), are used in the diagnosis and staging of prostate cancer. However, histopathological examination is considered a reliable method because of its visual characteristics and is regarded as the gold standard.<sup>2,3,7</sup>

In histopathological studies, tissue sections are examined in detail under a microscope by a histopathologist to evaluate cellular morphology, tissue organization, and pathological changes. While pathologists evaluate histological sections under a light microscope using morphological criteria, technological advances have enabled the integration of whole-slide imaging (WSI) systems into clinical practice. These systems enable the digitization of glass slides using high-resolution optical scanners, allowing images to be archived, analyzed, and shared in a digital environment and thereby facilitating the transition to the digital pathology paradigm in the diagnostic workflow.<sup>8</sup> WSI systems have enabled the integration of artificial intelligence (AI)-based analytical approaches aimed at reducing the subjectivity and interobserver variability encountered in conventional histopathological evaluations. This digital transformation contributes to optimizing diagnostic accuracy and clinical consistency by providing a more objective, rapid, and reproducible decision-support infrastructure for prostate cancer diagnosis.<sup>9</sup> AI algorithms show considerable potential for the histopathological grading of prostate cancer, particularly in radical prostatectomy specimens and needle biopsy samples.<sup>3</sup> Growing evidence in the current literature confirms that AI integration has the potential to optimize every stage of imaging-based diagnostic processes for prostate cancer.<sup>10,11</sup>

This article reviews recent studies on the analysis of histopathological images of prostate cancer and AI-based applications. The first section of the study provides information on prostate cancer and histopathological images. Subsequent sections first provide information on recently published studies involving AI-based analysis of histopathological images. The methodological approaches used in these studies and the AI algorithms applied to prostate cancer diagnosis are then discussed. Finally, the analysis of the studies discussed, their integration with decision-support systems, the limitations of machine learning- and deep learning-based studies for diagnosing prostate cancer from histopathological images, and potential directions for future research are addressed.

## METHODS

### Research Methodology and Analysis of Current Studies

The studies examined within the scope of this work were published in English between 2021 and 2025 in high-quality journals (Q1 or Q2 impact factor) included in the Science Citation Index Expanded (SCI-E). Therefore, journal articles and conference papers outside the scope of SCI-E were not included in the review. To identify the studies examined as part of this research, the keywords “histopathological image analysis, prostate cancer diagnosis, Gleason grading, artificial intelligence, machine learning, and deep learning” were searched in databases such as Google Scholar, Web of Science (WoS), PubMed, and Scopus. The literature reviewed within the scope of the study primarily focused on clinical diagnostic tasks such as the automatic detection of prostate cancer and disease staging through Gleason grading. Because the focus was strictly limited to prostate cancer diagnosis and Gleason grading based on histopathological images, studies involving other diagnostic methods, such as MRI, ultrasound, and CT, were not included. The detailed literature review, duplicate record removal, and article selection steps applied during the systematic review process are presented in Appendix 1 in accordance with PRISMA 2020 standards.<sup>12</sup> The methodological approaches, artificial intelligence architectures, datasets,

and performance results of the 12 original studies examined within the scope of this review are systematically summarized in Table 1 to provide a comparative analysis.<sup>5,8,11,13–21</sup>

### Analysis of Histopathological Images and Artificial Intelligence Approaches

Digital histopathology is a contemporary and innovative approach that represents a significant evolution in modern medicine and enables access to a large number of images for automated analysis. With the support of software tools, it enables the visualization and interpretation of cell and tissue samples in high-resolution images.<sup>22,23</sup> This has ushered in a new era in the development of analytical techniques that assist clinicians and support the quantification of image features. With the development of WSI technology, advanced artificial intelligence systems are being developed to extract features from tumors and their surrounding microenvironments that can predict clinical outcomes. Because of differences in slide preparation processes and technical variability arising from the complex architecture of tumor tissues, integrating computer-aided diagnosis (CAD) systems into routine clinical diagnosis is not a simple process.<sup>10</sup> The success of image analysis techniques depends directly on the quality of digital slide images. Various challenges exist in this process, including excessively large image sizes, insufficiently labeled data, image artifacts, heterogeneity among the images to be analyzed, color variations, and histological artifacts.<sup>2,23</sup> CAD systems designed to overcome these obstacles can be used with high accuracy in the diagnosis of PCa and similar cancer types. The basic stages and design of the CAD system are presented in Figure 1.

### Preprocessing in Histopathological Images

Methods commonly used during the preprocessing of histopathological images for noise reduction and detail enhancement include mean, median, adaptive mean, adaptive median, and Gaussian smoothing filters. These techniques eliminate unwanted noise from the images.<sup>2,24</sup> The patch technique is used in studies to overcome difficulties arising from the large size of the images. This technique divides images into regions called patches, typically consisting of 1024×1024 pixels. This enables the identification of relevant areas.<sup>25</sup>

Segmentation is another process applied to images. Through segmentation, digital images with similar color tones can be divided into meaningful subregions. Segmentation techniques are generally based on thresholding, region-based, edge-based, or machine learning methods.<sup>2,24</sup> In histopathological images with complex tissue structures, such as those of prostate cancer, four basic tissue components (nucleus, stroma, lumen, and epithelium) have been segmented.<sup>25</sup> This

enables the transition from multiple nuclear components to independent components.<sup>26</sup>

Image and color normalization is another applied step. This process is a fundamental preprocessing step used to eliminate color and contrast variations arising from different laboratories, scanners, or staining processes. Another process applied during image normalization is histogram equalization. In histopathological analyses, histogram equalization and histogram matching methods are widely used to eliminate color variations arising from lighting conditions and staining processes.<sup>24,27</sup>

Data augmentation is another preprocessing step that must be performed before proceeding to feature extraction and classification. This method enables the creation of a more stable classifier model by reducing class imbalance. In recent years, AI-based methods such as generative adversarial networks (GANs) have also been proposed, enabling the automatic optimization of various training hyperparameters in data augmentation strategies. These approaches reduce the need for manual intervention by determining the most efficient augmentation configurations specific to the model and improve the overall performance of the system.<sup>28</sup> The stages and methods of image preprocessing in histopathological image analysis are presented in Table 2. Image examples illustrating the application of these methods are shown in Figure 2.

### Feature Extraction

Feature extraction is a crucial step for the successful and appropriate application of the preprocessing stages. Feature extraction methods and their subtechniques for the histopathological image analysis of prostate cancer are presented in Table 3. Texture-based features can be obtained by analyzing statistical, structural, or spectral patterns that reflect density changes across the image surface and relationships between pixels. Studies have generally preferred texture-based methods such as the gray-level co-occurrence matrix (GLCM), gray-level run-length matrix (GLRLM), local binary pattern (LBP), and fractal dimension.<sup>24,29</sup> Color-based features provide basic information about the intensity distributions and spectral characteristics of pixels within the region of interest (ROI). Feature extraction and selection processes in this category utilize different color spaces to distinguish tissue components. The pixel-based color moment descriptor (PCMD) feature is frequently preferred in studies.<sup>29</sup> Morphological features are derived from the shape and structure of histopathological images. To represent the cancerous region, features such as area, perimeter, maximum and minimum radius, equivalent diameter, circularity, and entropy are extracted.<sup>24,30</sup>

| Table 1. Comparative analysis of the studies examined within the scope of this review |                                                                       |                                                                                 |                                                                  |                                                                           |                                                                                                                                                                |
|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                                                                 | Dataset                                                               | Methodology                                                                     | Clinical focus                                                   | Performance metrics                                                       | Contribution/result                                                                                                                                            |
| Kott et al. <sup>5</sup>                                                              | 85 biopsies from 25 patients; 14,803 256×256-pixel image patches      | Convolutional neural network (CNN) and 5-fold cross-validation                  | Cancer detection and Gleason grading (3, 4, and 5)               | Accuracy: 91.50%; Precision: 0.93                                         | Reduced interobserver variability and the risk of diagnostic error.                                                                                            |
| Singhal et al. <sup>8</sup>                                                           | Thousands of biopsy slides (WSIs) from different centers              | Deep learning model                                                             | Objective Gleason grading                                        | Accuracy: 83%–89%                                                         | The objectivity and generalizability of the model were demonstrated using large multicenter datasets.                                                          |
| Bulten et al. <sup>11</sup>                                                           | 160 biopsy samples                                                    | AI-based decision-support system                                                | Gleason grading                                                  | Cohen's kappa: 0.82                                                       | The use of artificial intelligence improved the consistency of Gleason grading among pathologists.                                                             |
| Pinckaers et al. <sup>13</sup>                                                        | 4,712 biopsy images                                                   | ResNet-34                                                                       | Cancer diagnosis using WSI                                       | Area under the curve (AUC): 99%                                           | Reduced GPU memory requirements by eliminating the need for manual pixel-level labeling.                                                                       |
| Duenweg et al. <sup>14</sup>                                                          | Digital histopathology images from 47 patients (31 training, 16 test) | ResNet-based deep learning and segmentation ensemble model                      | Detection of cancer areas and discrimination of Gleason patterns | Accuracy: 88%–89% for both models                                         | Although both models were successful in cancer detection, ResNet demonstrated superior performance over the ensemble model in distinguishing Gleason patterns. |
| Raciti et al. <sup>15</sup>                                                           | 610 needle biopsy WSIs                                                | Artificial intelligence-supported classification using hybrid models            | Classification of all histological grades and tumor sizes        | Classification accuracy: 100%                                             | AI support achieved complete classification accuracy (100%) across all WSIs, regardless of tumor size.                                                         |
| Mun et al. <sup>16</sup>                                                              | 6,664 and 936 needle biopsy WSIs                                      | Automated Gleason grading system (YAAGGS) using weakly supervised deep learning | Automated Gleason grading and classification                     | Accuracy: 77.50%                                                          | Automated end-to-end grading was performed on a large WSI dataset.                                                                                             |
| Jung et al. <sup>17</sup>                                                             | 593 independent WSI slides                                            | DeepDx artificial intelligence system                                           | Cancer detection and Gleason scoring analysis                    | Accuracy similar to pathology reports; higher agreement in Gleason scores | Independent datasets confirmed that the DeepDx system achieved greater grade-group agreement than pathologist reports.                                         |
| Huang et al. <sup>18</sup>                                                            | 1,000 WSI samples obtained from 589 patients                          | Deep neural network-based artificial intelligence                               | High-efficiency prostate cancer detection                        | AUC: 92%                                                                  | High diagnostic accuracy and efficiency were achieved in a large patient cohort.                                                                               |

**Table 1 (cont).** Comparative analysis of the studies examined within the scope of this review

| Study                      | Dataset                  | Methodology                                                              | Clinical focus                                      | Performance metrics                      | Contribution/result                                                                                                                                                                                             |
|----------------------------|--------------------------|--------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Xiang et al. <sup>19</sup> | 6,174 WSIs               | Graph convolutional network                                              | Gleason grading                                     | AUC: 99.20%                              | Cellular relationships were modeled by representing each whole-slide image as a graph structure.                                                                                                                |
| Liang et al. <sup>20</sup> | Test dataset of 531 WSIs | Attention mechanism-based LSTM                                           | Segment-based feature extraction and classification | Cohen's kappa: 0.93                      | Digital diagnostic pathology demonstrated strong generalizability in automatically extracting prostate cancer grading information and addressing a critical gap in pathologist expertise.                       |
| Kabir et al. <sup>21</sup> | 2,699 clinical cases     | 3-stage DL system: patch classification, segmentation, and random forest | Automated Gleason grading estimation                | F1 score: 83.80%;<br>Cohen's kappa: 0.92 | Combined deep learning-based segmentation with the traditional random forest algorithm, providing a promising prognostic approach capable of efficiently and reliably generating clinically meaningful results. |

Classification Process

Artificial intelligence is a field that mimics human intelligence to solve complex problems and relies on data-driven modeling. Machine learning, one of the cornerstones of this field, enables systems to recognize patterns in data without being explicitly programmed, while deep learning (DL) extracts information directly from data through multilayer neural networks.<sup>31,32</sup> While the manual definition and extraction of features are prerequisites in studies based on traditional machine learning algorithms, feature extraction and classification processes in deep learning approaches are performed automatically through an end-to-end architecture that learns directly from the data. The cross-validation process applied during the classification stages, consisting of training, validation, and testing phases, is shown in Figure 3.

Traditional machine learning algorithms used in studies diagnosing PCa from histopathological images include support vector machines, artificial neural networks, k-nearest neighbors, random forests, and boosting-based methods.<sup>2</sup> Numerous studies have been conducted using different neural networks, such as convolutional neural networks (CNNs), deep neural networks, and GANs, for PCa diagnosis from histopathological images. However, CNNs are among the most frequently preferred algorithms in these studies.<sup>33</sup> Examination of the literature shows that CNN architectures with different structural depths and parameter characteristics, such as AlexNet, ResNet, VGGNet, SqueezeNet, and DenseNet, are commonly preferred.

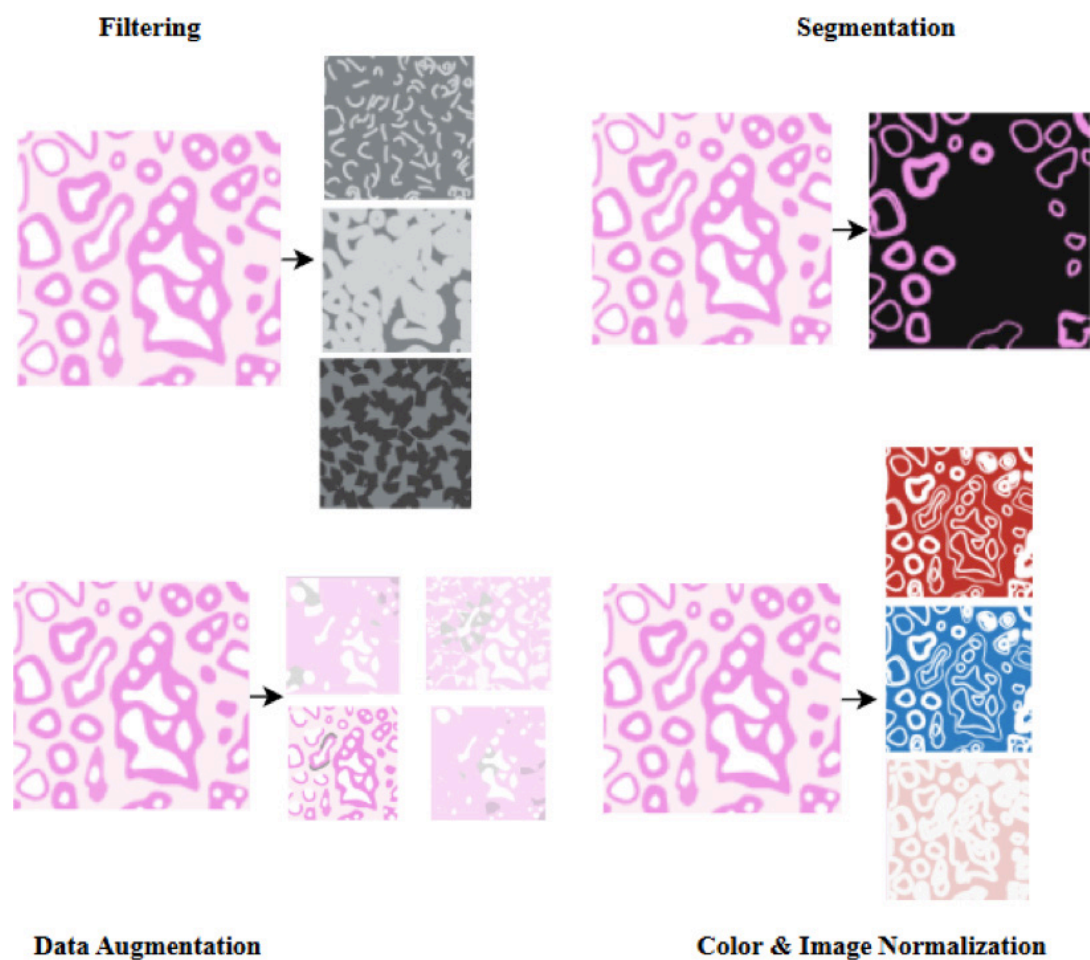
Performance Evaluation Criteria

In machine learning- and deep learning-based classification studies, various performance metrics are used to measure the accuracy and reliability of models. These metrics enable the model's predictive ability to be evaluated from different perspectives. Expressing a model's performance using a single metric is insufficient to reflect all characteristics of the system. Therefore, to summarize the real-world performance of models that have completed the training process, multidimensional metrics should be reported using an independent test dataset.<sup>31,34</sup> The key metrics used to evaluate classification performance, particularly in studies diagnosing prostate cancer from histopathological images, are accuracy, F1 score, area under the curve (AUC), and kappa statistics.

RESULTS

Analysis of the Studies

In recent years, interest in artificial intelligence-based systems and computer-aided diagnosis systems for prostate cancer diagnosis has increased significantly, particularly in pathology and various imaging modalities.<sup>35</sup> Artificial

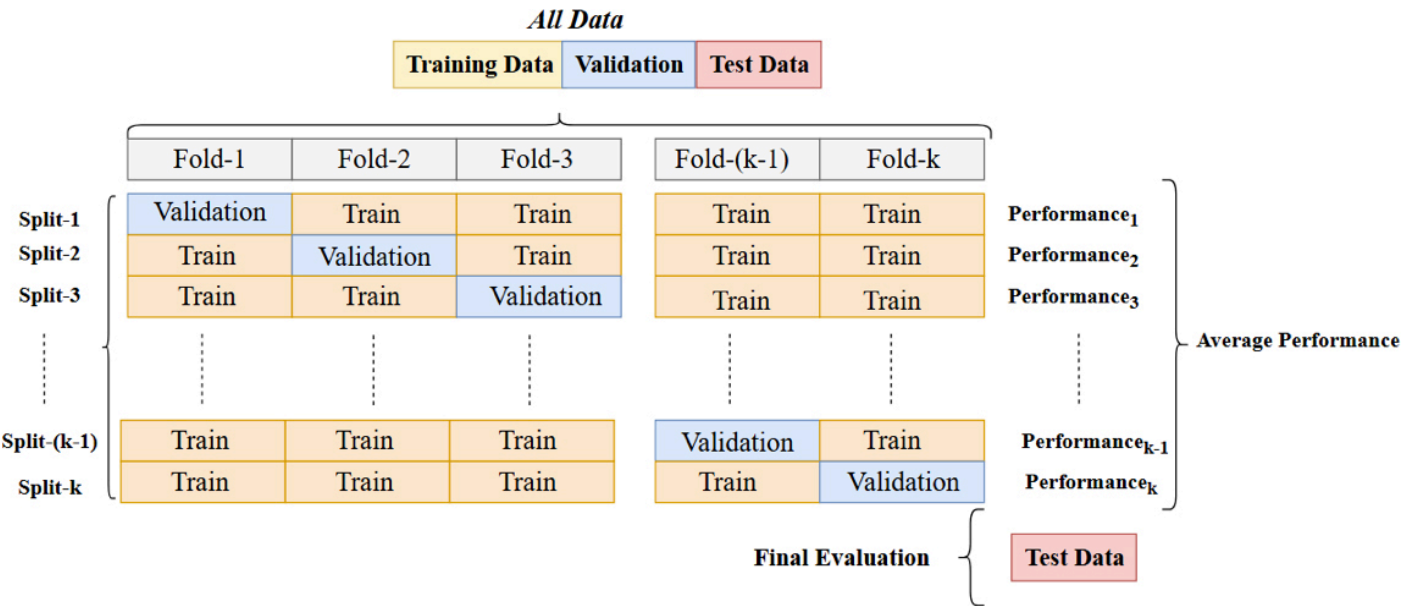


**Figure 2.** Example of image preprocessing steps applied to a histopathological image.

| Table 2. Image preprocessing stages and methods in histopathological image analysis |                        |                                       |                                     |
|-------------------------------------------------------------------------------------|------------------------|---------------------------------------|-------------------------------------|
| Filtering                                                                           | Segmentation           | Data augmentation                     | Color and image normalization       |
| Mean                                                                                | Thresholding           | Geometric transformations             | Histogram equalization and matching |
| Median                                                                              | Region-based           | Photometric transformations           |                                     |
| Adaptive mean/median                                                                | Edge-based             | Artificial intelligence-based methods |                                     |
| Gaussian smoothing                                                                  | Machine learning-based |                                       |                                     |

intelligence applications in prostate cancer pathology play an important role in digital pathology, diagnostic medicine, and precision oncology.<sup>31</sup> The high-dimensional complexity and morphological variability inherent in histopathological images make this field particularly suitable for computational analysis. This review also focuses on studies investigating AI-based diagnosis and CAD systems for prostate cancer using histopathological images. With this focus, the architectures, dataset sizes, and diagnostic performance of studies conducted between 2021 and 2025, whose results are summarized in

Table 1, were evaluated. As a result of this evaluation, the methods applied in these studies were discussed in detail in the previous section. The high information density of digital histopathological images for diagnostic purposes makes this field an ideal area of research for machine learning.<sup>36,37</sup> However, studies in the literature indicate a shift toward deep learning methods rather than traditional machine learning approaches. Among DL methods, CNN-based approaches have been preferred more frequently.<sup>13,14,19</sup> Previous studies have also demonstrated that DL techniques can accurately



**Figure 3.** Cross-validation method used in the classification process.

**Table 3.** Feature extraction methods and subtechniques in histopathological image analysis of prostate cancer

| Texture-based     | Color-based                                                         | Morphological and topological |
|-------------------|---------------------------------------------------------------------|-------------------------------|
| GLCM              | PCMD                                                                | Size and area                 |
| GLRLM             | Statistical features (mean, standard deviation, kurtosis, skewness) | Shape factors                 |
| LBP               | Color space conversions                                             | Boundary irregularity         |
| Fractal dimension | Color histograms and moments                                        | Cell graphs                   |

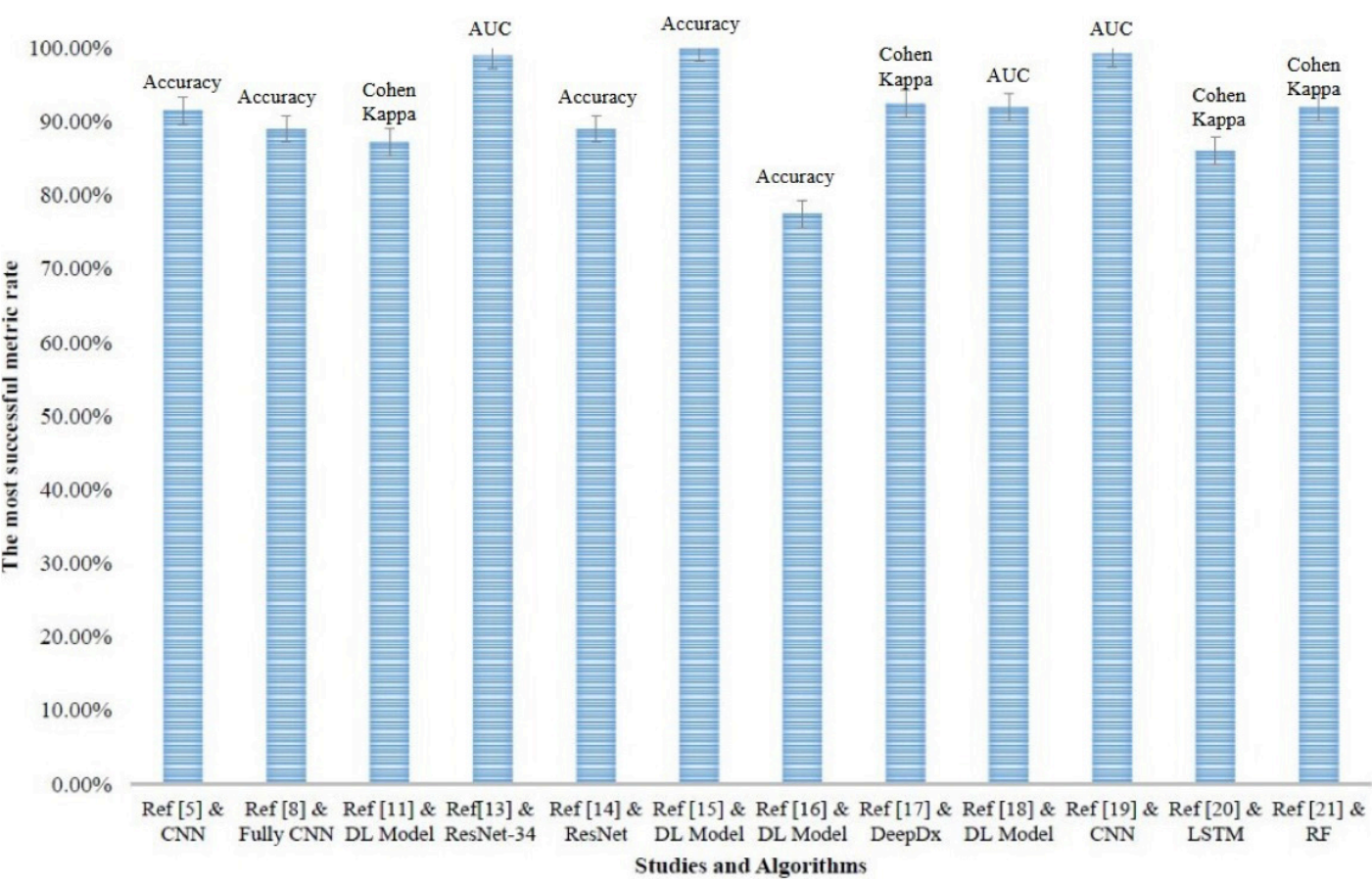
GLCM: Gray-level co-occurrence matrix; GLRLM: Gray-level run-length matrix; LBP: Local binary pattern; PCMD: Pixel color moment descriptor.

detect cancer in histopathological images.<sup>38</sup> The main reason for this trend may be that, unlike traditional machine learning approaches, which are limited by their reliance on feature extraction processes, deep learning models can directly process latent features in complex tissue images and analyze them hierarchically.

When the performance evaluation processes of the reviewed studies are analyzed, accuracy, AUC, and kappa statistics are commonly used to assess model performance. In a field such as prostate cancer, where clinical decision-making is critical, focusing solely on accuracy rates can be misleading. In this context, the emphasis on AUC values in the reviewed studies demonstrates the balance between sensitivity and specificity and reflects the discriminatory power of the models across pathological classes. High AUC values indicate a strong ability of the models to discriminate between complex histopathological tissue patterns. Kappa

statistics, on the other hand, provide scientific evidence of the level of agreement between artificial intelligence and expert pathologists while accounting for agreement occurring by chance. The consistency of these metrics reinforces the reliability of the developed algorithms as clinical decision-support mechanisms. The algorithms that achieved the best performance in the reviewed studies, together with their accuracy, AUC, or kappa values, are presented in Figure 4.

The findings from the reviewed studies demonstrate that artificial intelligence applications in prostate cancer pathology provide strategic advantages in terms of speed, objectivity, and diagnostic consistency. The Gleason grading system, which is the focus of numerous studies, is being transformed from a traditional and subjective evaluation process into a data-driven and standardized framework through the integration of artificial intelligence. The results



**Figure 4.** Distribution of algorithms used and their reported performance in the reviewed studies.

indicate that artificial intelligence is not merely a tool for accelerating workflow but also has the potential to reduce differences in interpretation among physicians and promote greater standardization in Gleason grading.

DISCUSSION

Despite the considerable potential offered by artificial intelligence in prostate cancer pathology, significant obstacles remain to the full integration of these systems into clinical practice. Legal and ethical concerns regarding patient data privacy are among the factors that hinder the establishment of clinical confidence. Although most of the current literature focuses on laboratory performance, logistical issues such as the robustness of these models across heterogeneous datasets, high storage costs, and practical integration into hospital workflows constitute major constraints on the widespread adoption of artificial intelligence as a diagnostic tool.<sup>23,39</sup> Limitations arising from these fundamental constraints are also evident in the studies presented in Table 1. As shown by the comparative results in Table 1, the wide variability in model performance stems

directly from challenges associated with large multicenter datasets, as well as from the multifactorial balance between the sensitivity of pathologist annotations and the complexity of model architectures. Most studies employ deep learning models or hybrid approaches that combine multiple models. Standard machine learning algorithms are preferred less frequently, mainly because deep learning methods generally achieve higher and more stable performance. As shown in Table 1 and Figure 4, a substantial proportion of existing studies focus on only a single evaluation metric. However, for a clinically reliable decision-support system, it is essential to assess all performance metrics jointly and ensure that they yield consistent and coherent results. Reliance on a single metric may lead to misleading interpretations. Although the success of artificial intelligence models in prostate cancer pathology depends directly on the quality of the training data, data bias and insufficient data volume are among the most fundamental problems in the current literature.<sup>3</sup> In a large proportion of studies, the limited size of the training set restricts the models’ ability to learn morphological variations across different populations and weakens the generalizability

of CAD systems. The enormous data burden resulting from dividing multiple biopsy samples from a single patient into millions of patches, together with the high computational cost required, is also considered a significant challenge. The use of WSI technology poses a substantial computational challenge because of the large volume of data. These images must be divided into smaller sections for analysis using current artificial intelligence methods.<sup>40</sup> In addition to the data burden, subjective differences in interpretation among experts in Gleason grading complicate the creation of the gold-standard datasets required for algorithm training. This critical need for high-quality, expert-annotated histopathological imaging data has led researchers to rely on established and more comprehensive open-access datasets in their studies. However, even these datasets have been reported to be limited and inconsistent. The most comprehensive histopathological dataset, frequently used and widely accepted in studies of Gleason grading and prostate cancer detection from histopathological images, was introduced through the Prostate Cancer Grade Assessment (PANDA) competition. This dataset consists of 12,625 prostate biopsy WSIs collected from six different centers.<sup>41</sup> Another histopathological image dataset, recently introduced into the literature by Koziarski and colleagues and still used in relatively few studies, is DiagSet. This dataset consists of more than 2.6 million tissue sections.<sup>42</sup> Other known publicly available datasets consisting of biopsy samples for PCa diagnosis include SICAP-MIL, Ibex, Gallo, and Tolkach.

A significant gap for future research is that most current deep learning approaches are trained on single-center datasets. This results in reduced model performance and limited generalizability when data from different centers are used, for example, data generated using different staining protocols, scanning devices, and clinical workflows. Therefore, there is a need for more robust models trained on multicenter datasets and validated using external datasets. In addition, the “black-box” nature of deep learning models constitutes another significant research gap in clinical applications. Particularly in critical pathological assessments such as Gleason scoring, the inability of pathologists to clearly identify the visual or histological features on which the model bases its decisions limits the reliability and acceptability of clinical decision-support systems. Considering these two fundamental problems together, the development and adaptation of explainable artificial intelligence (XAI) methods in pathology represent an important research need. XAI-based approaches can increase clinician confidence by making model decisions more transparent and can also facilitate the clinical integration of AI-powered diagnostic systems.

## CONCLUSION

In conclusion, WSI technology serves as a critical and promising tool in diagnostic pathology by transforming traditional microscopic examination into a digital ecosystem, thereby enabling the development and clinical integration of high-performance artificial intelligence algorithms. The high-resolution digital data obtained through WSI preserve microscopic details of tissue architecture and allow deep learning models to perform hierarchical feature learning on large-scale datasets. The reviewed studies demonstrate that artificial intelligence has strong potential to support expert pathologists' decisions, particularly in Gleason grading and cancer detection. However, for these models to be fully integrated into routine clinical laboratories, methodological challenges such as dataset diversity, model interpretability, and high computational costs must be addressed. The adoption of these technologies within the digital pathology ecosystem will be a critical step toward advancing precision oncology in future research, provided that these clinical and technical bottlenecks are resolved.

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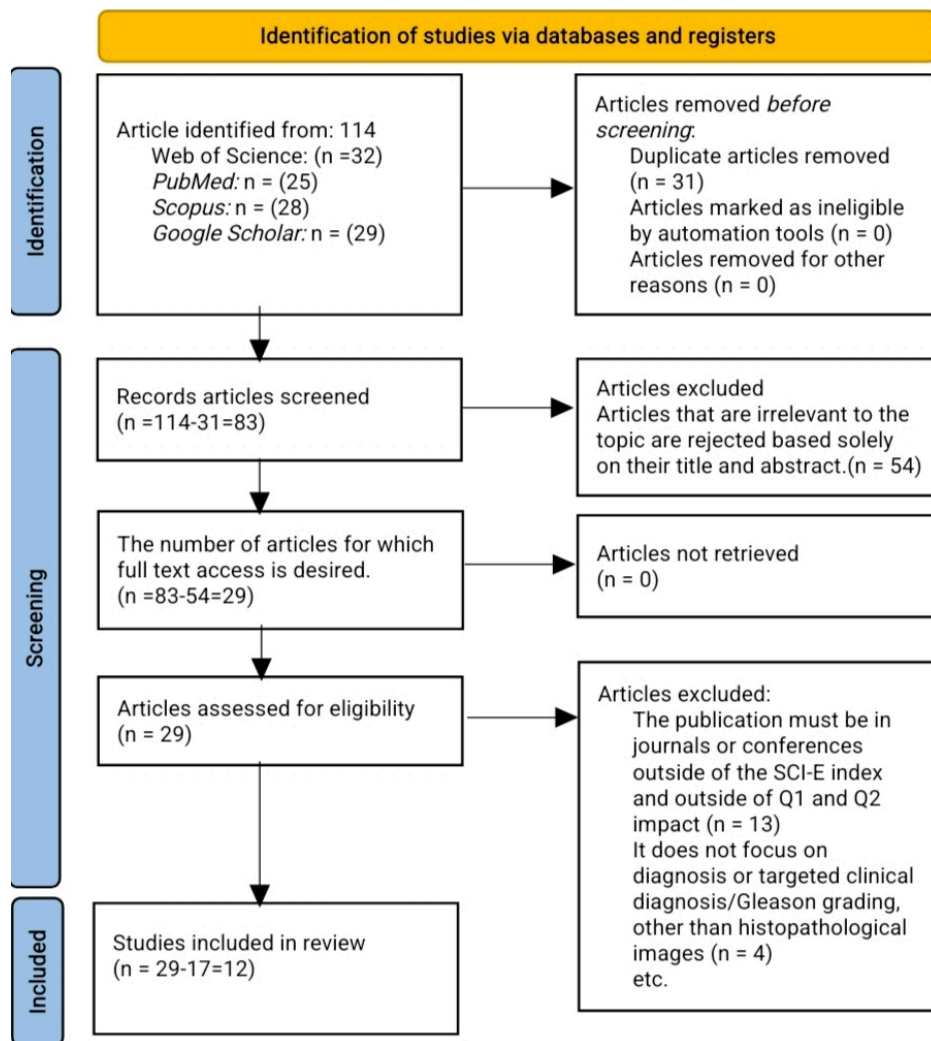
**Peer-review:** Externally peer-reviewed.

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**Appendix 1.**