



Artificial intelligence in digital pathology of cutaneous lymphomas: A review of the current state and future perspectives

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ABSTRACT

Primary cutaneous lymphomas (CLs) represent a heterogeneous group of T-cell lymphomas and B-cell lymphomas that present in the skin without evidence of extracutaneous involvement at time of diagnosis. CLs are largely distinct from their systemic counterparts in clinical presentation, histopathology, and biological behavior and, therefore, require different therapeutic management. Additional diagnostic burden is added by the fact that several benign inflammatory dermatoses mimic CL subtypes, requiring clinicopathological correlation for definitive diagnosis. Due to the heterogeneity and rarity of CL, adjunct diagnostic tools are welcomed, especially by pathologists without expertise in this field or with limited access to a centralized specialist panel. The transition into digital pathology workflows enables artificial intelligence (AI)-based analysis of patients' whole-slide pathology images (WSIs). AI can be used to automate manual processes in histopathology but, more importantly, can be applied to complex diagnostic tasks, especially suitable for rare disease like CL. To date, AI-based applications for CL have been minimally explored in literature. However, in other skin cancers and systemic lymphomas, disciplines that are recognized here as the building blocks for CLs, several studies demonstrated promising results using AI for disease diagnosis and subclassification, cancer detection, specimen triaging, and outcome prediction. Additionally, AI allows discovery of novel biomarkers or may help to quantify established biomarkers. This review summarizes and blends applications of AI in pathology of skin cancer and lymphoma and proposes how these findings can be applied to diagnostics of CL.

1. Introduction

Primary cutaneous lymphomas (CLs) are a group of non-Hodgkin lymphomas presenting in the skin without extracutaneous disease at the time of diagnosis. CLs are recognized to have different clinical behavior and prognosis compared with systemic lymphomas with similar histological features [1]. The diagnoses of CLs, considered to be at the interface between dermatopathology and hematopathology, can be very difficult, in part due to their heterogeneity. Additionally, there is

considerable overlap of clinical and histopathological features of CL entities and benign inflammatory dermatoses (BIDs) [2]. Therefore, there is a strong dependency on clinicopathological correlation for a definite diagnosis. Due to their rarity, referral of (suspected) CL patients to an expert center for skin lymphoma is recommended for diagnostic and/or treatment purposes [3]. Not surprisingly, adjunct diagnostic tools to aid pathologists within but also outside these referral centers are particularly welcomed.

The promising field of digital pathology (DP) had rapidly expanded

Abbreviations: AI, artificial intelligence; AUC, area under the curve; BCC, basal cell carcinoma; BD, Bowen's disease; BID, benign inflammatory dermatosis; BL, Burkitt lymphoma; C-ALCL, primary cutaneous anaplastic large-cell lymphoma; CBCL, cutaneous B-cell lymphoma; CL, cutaneous lymphoma; CLL, chronic lymphocytic leukemia; CNN, convolutional neural network; CTCL, cutaneous T-cell lymphoma; DL, deep learning; DLBCL, diffuse large B-cell lymphoma; FH, follicular hyperplasia; FL, follicular lymphoma; LH, lymphoid hyperplasia; MF, mycosis fungoides; PCFCL, primary cutaneous follicle center lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; ROI, region of interest; SCC, squamous cell carcinoma; SLL, small lymphocytic leukemia; SS, Sézary syndrome; WSI, whole-slide image.

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after the introduction of whole slide scanners about two decades ago, allowing the complete digitization of glass microscopic slides traditionally used in diagnostics. A large clinical study led to the permitted marketing by the U.S. Food and Drug Administration (FDA) for the first *whole-slide imaging* (WSI) system for reviewing digital pathology slides [4]. Multiple validation studies have since examined the use of WSIs for primary diagnostics in dermatopathology, yielding encouraging results with high concordance between light microscopy and WSI diagnosis, for both skin biopsies and skin excisions [5–10] and diagnosis of lymphoma on biopsy and resection specimens of lymph nodes and extranodal locations [11]. In particular, WSI diagnosis did not hinder accurate differentiation between spongiotic dermatitis and mycosis fungoides, the most common variant of CL [8]. In recent years, DP is increasingly being adopted in several countries for routine histologic diagnosis [10] and serves as a platform for the use of *artificial intelligence* (AI) and *deep learning* (DL)-based algorithms. For a compilation of terminology definitions in AI, we direct the reader to [Supplementary Table 1](#).

DL is a branch of *machine learning* that utilizes multilayered neural networks to create algorithms capable of processing and extracting meaningful patterns from vast volumes of data. The integration of DL tools in the DP workflow offers many formulated possibilities to assist pathologists in tasks including, but not limited to, cancer detection and classification, quantification and measurement, grading of disease severity, prediction of treatment response, and even identification of novel morphological features with prognostic implications [12]. Most recent studies exploring AI applications have focused on the major cancer types, such as lung, breast, and colon cancer, with clear underrepresentation of rare diseases. Paradoxically, rare diseases, including CLs, might benefit most from DP and AI-assisted tools, since most pathologists will have limited experience with them and diagnosis can be challenging.

To date, a literature search reveals minimal investigation for AI applications in DP of CLs. In order to bring about change, we review the current state of affairs but have as our primary objective the exploration of potential applications of AI within the histopathology of CLs, building on recent peer reviews and editorials on the applications of AI in dermatopathology [13–15] and pathology of systemic/nodal lymphoma [16,17]. In this review, we discuss how a synergy between previous works in other skin cancers and systemic lymphomas could be adapted for use in the diagnosis and differentiation of CL from benign mimics and subclassification of the many subtypes of CL. Next, we explore the use of DL for the identification of biomarkers for progression and survival, as well as prediction of therapy response, followed by the quantification of established biomarkers (Fig. 1, Table 1). Finally, we conclude with the limitations of AI in the context of CL and share our future perspectives.

2. Diagnosis of CL and distinction from reactive infiltrates

In contrast to basal cell carcinoma (BCC), melanocytic tumors, and systemic lymphomas, as will be discussed later, only three preliminary works could be identified for DL-based approaches in diagnostic pathology of CLs. The differentiation of early-stage mycosis fungoides (MF) versus benign inflammatory dermatoses (BIDs) remains a significant challenge due to overlapping clinical and histopathological features. However, an early and correct diagnosis may have important treatment implications, such as avoiding incorrect treatment and negatively affecting eventual clinical outcomes, underlining the relevance of this task as a potential application for DL.

Kicking off in CL, colleagues from Switzerland published a DL-aided diagnostics tool for predicting MF or eczema using WSIs and a corresponding segmentation maps of epidermis and ‘spongiosis’ tissue as input [18]. However, on a dataset of 209 WSIs of eczema and 98 WSIs of MF from a total of 93 patients, the classification accuracy showed an almost negligible difference compared with a dummy classifier. Consequently, this study highlights the need for significant improvements in this area of research.

In a pilot study from our group [19], *weakly supervised models* were trained for the differentiation of early MF and BIDs on a dataset containing 580 WSIs from 177 MF patients and 165 BID patients. This approach achieved a mean slide-level classification accuracy of 75.9%, which was comparable with the performance of two expert pathologists. The results presented here are preliminary and await external validation. One of the strengths of our results lies in the inclusion of both unequivocal and equivocal cases in the dataset, which were sent in for consultation. Additionally, the ground-truth labels, i.e., the diagnoses, for MF and challenging MF mimics were obtained after clinicopathological correlation in an expert panel.

Finally, Zheng and colleagues [20] developed a novel method based on the ResNet-34 *convolutional neural network* (CNN) for the detection of neoplastic cells in primary cutaneous CD30-positive lymphoproliferative disorders based on CD30 expression. For this, they used a small dataset of 28 patients with lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma (C-ALCL). The approach of using a specific biomarker, such as CD30, to identify the presence of neoplastic cells, however, is not feasible for most other CL subtypes with none to variable levels of CD30 expression and the lack of other clear-cut immunohistochemical biomarkers.

In the systemic lymphoma-field, several studies included reactive lymph nodes in their datasets, to aid in the distinction between lymphoma and reactive conditions. In contrast to diffuse large B-cell lymphoma (DLBCL), composed of a diffuse proliferation of neoplastic centroblasts and immunoblasts, the distinction of follicular lymphoma (FL) from follicular hyperplasia (FH) can be a diagnostic challenge due to overlapping morphological features. In the skin, the same accounts for the distinction of primary cutaneous follicle center lymphoma (PCFCL) with a follicular growth pattern versus benign lymphoid hyperplasia and to a lesser extent primary cutaneous marginal zone lymphoma, the latter to be interpreted as a lymphoproliferative disorder due to its indolent clinical course [21].

To this end, AI technology was reported by Miyoshi et al. to outperform seven pathologists, including an experienced hematopathologist, when distinguishing nodal and extranodal DLBCL, FL, and reactive lymphoid hyperplasia. In this study, cropped images from the lesional area of the H&E-stained WSI, annotated by a hematopathologist, were used to train an ensemble classifier, which averaged the scores of 15 classifiers to make final predictions. In test sets made up of 100 image patches with magnifications of $\times 5$, $\times 20$, and $\times 40$, the AI classifier achieved an accuracy of 97% compared with a maximum individual accuracy of 76% for the seven pathologists [22]. In addition, Syrykh et al. trained several deep CNNs to distinguish FL from FH in lymph nodes based on H&E-stained WSIs. The authors collected a total of 378 lymph nodes from two French pathology departments, including 197 lymph nodes with FL. For slide-level diagnosis, the models achieved area under the curves (AUCs) between 0.92 and 0.99 depending on the resolution level, reaching the best performance at the lowest resolution [23].

So far, the results obtained for the classification of LH and various non-Hodgkin B-cell lymphomas in lymph nodes are not disappointing. These findings support the notion that DL can potentially assist pathologists in classifying cutaneous B-cell lymphoma (CBCL) and benign lymphoid hyperplasia/cutaneous pseudolymphomas. Conversely, propositions for DL in T-cell lymphomas, which constitute the majority of CLs in contrast to nodal lymphomas that are mostly of B-cell origin, are strongly underrepresented.

In line with these studies distinguishing lymphomas from reactive infiltrates, we envision the development of an automated DL-based tool for triaging of skin biopsies for CL for widespread use in pathology laboratories. Such a screening tool would have many benefits, including the reduction of turnaround time, saving tissue for additional immunohistochemistry staining, and timely referral to specialized CL centers. In other skin cancers, a pathology DL system was already proposed for the hierarchical classification of skin specimen WSIs into six classes,

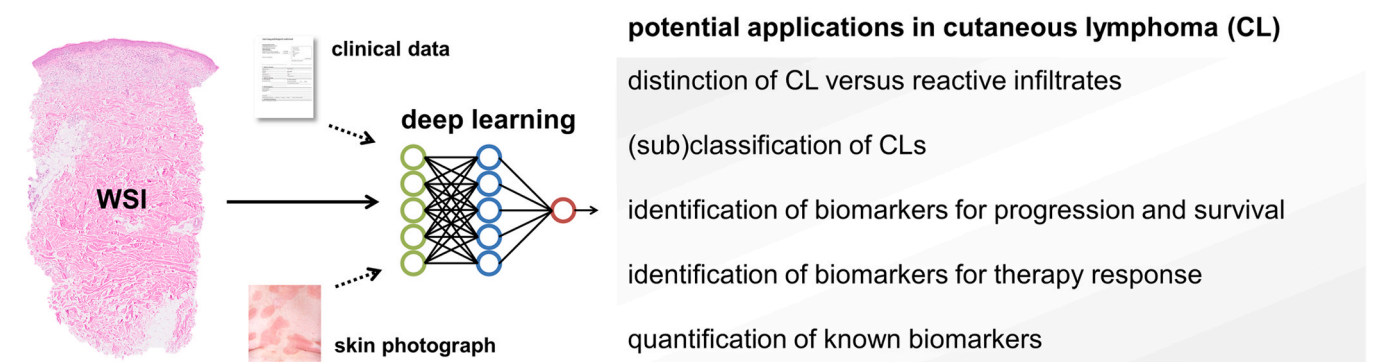


Fig. 1. Overview of potential applications of artificial intelligence in pathology of cutaneous lymphomas. Abbreviations: CL, cutaneous lymphoma; WSI, whole-slide image.

including basaloid, squamous, melanocytic low-, intermediate-, or high-risk, and other specimens. This system was able to sort and triage ‘melanocytic suspect’ specimens with a high AUC value of 0.93 and maintained high performance when applied to datasets from two validation labs [24]. In addition, Ianni et al. [25] proposed a DL system composed of a cascade of three independent CNNs for the classification of a wide variety of dermatopathology WSIs into one of four histological classes, consisting of basaloid, melanocytic, squamous, and other

entities. On an independent test set originating from 3 laboratories with different scanners and staining protocols, a specimen-level accuracy of 78% was achieved. When confidence score thresholds were used for model decisions, the accuracy increased to up to 98%. Although these two studies did not include a lymphoid class, they do illustrate that it might be possible to have a DL system triage ‘suspect’ lymphoid proliferation to a skin lymphoma expert, or label them as suspected. This approach could reduce the number of misdiagnosed CL patients and

Table 1
Overview of the potential applications of artificial intelligence in the pathology of cutaneous lymphomas. Abbreviations: BCC, basal cell carcinoma; BID, benign inflammatory dermatosis; BL, Burkitt lymphoma; C-ALCL, cutaneous anaplastic large cell lymphoma; CL, cutaneous lymphoma; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FH, follicular hyperplasia; FL, follicular lymphoma; LyP, lymphomatoid papulosis; MF, mycosis fungoides; MCL, mantle cell lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicle center lymphoma; SCC, squamous cell carcinoma; SS, Sézary syndrome; WSI, whole-slide image.

Potential applications in CL pathology	Illustrative proof-of-concepts in dermatopathology and hematopathology
<i>The distinction of CL versus reactive infiltrates, for example:</i>	
-Classifying between early-stage MF and BIDs.	The detection of basal cell carcinoma in skin histology [29,30,36–38,81]
-Classifying between PCFCL, PCMZL and benign lymphoid hyperplasia.	The hierarchical classification of skin specimen WSIs into separate classes, including basaloid, squamous, melanocytic, and other entities [24,25] Classifying between MF and BIDs in skin histology [18,19] Classifying between FL and FH in lymph nodes [23] Classifying between nodal SLL/CLL, BL, DLBCL, FL and reactive lymph nodes [22,58,59,82,83] Locating CD30-positive tissue regions in LyP and C-ALCL [20]
<i>The (sub)classification of CLs, for example:</i>	
-Classifying between LyP and more aggressive CTCL.	Classifying melanoma versus nevus, as well as distinguishing Spitz nevus from conventional nevus, in both skin excisions and biopsies [42,44,45,47,48,80,84]
-Classifying between PCDLBCL-LT and PCFCL with a diffuse growth pattern.	Distinguishing between two intra-epidermal lesions: Bowen’s disease and seborrheic keratosis [40] Performing a binary classification task to distinguish nodular BCCs, dermal nevi, and seborrheic keratoses from various ‘distractors’ to classify each common skin lesion accurately [39] Classifying between three non-Hodgkin lymphoma subtypes (CLL, FL, and MCL) [56,85,86]
<i>The identification of biomarkers for progression and survival, for example:</i>	
-Identifying morphological characteristics linked to an unfavorable outcome in MF.	Detecting MYC translocation in DLBCL [67]
-The identification of genetic alterations in PCDLBCL-LT.	Predicting the presence of mutated BRAF in WSIs of primary melanoma [68] Predicting the likelihood of rapid metastasis or no metastasis at all in primary cutaneous SCC [63] Predicting visceral recurrence and disease specific survival in early-stage melanoma [64] Predicting sentinel lymph node status from H&E slides of primary melanoma [65]
<i>The identification of biomarkers for therapy response, for example:</i>	
-Predicting the response to anti-PD-1 and anti-CD30 therapy in advanced-stage MF and SS.	Predicting the anti-PD-1 response in advanced melanoma on routine H&E-stained slides [72] Predicting immune checkpoint inhibitor treatment outcome in metastatic melanoma based on integrated WSI and patient clinicodemographic variables [53]
<i>The quantification of established biomarkers, for example:</i>	
-The standardization of CD30 reporting.	The automated computation of the proliferation index using the Ki-67 immunohistochemical stain in lymph node metastases of melanoma [74]
-The automated calculation of the Ki-67 proliferation index.	

improve the turnaround time.

3. (Sub)classification of CLs

As mentioned above, CLs are a heterogeneous group of cutaneous T-cell lymphomas (CTCL) and CBCL with multiple distinct pathologic entities and a wide array of clinical and immunophenotypic features [26,27]. Clinicopathological correlation is often essential for reaching a correct diagnosis since CLs may have overlapping histomorphological features but also display markedly different clinical behaviors ranging from indolent to very aggressive [28]. For example, it is important to recognize the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders with a generally indolent behavior, to prevent misdiagnosis of more aggressive types of CTCLs, such as MF with large-cell transformation [27]. Likewise, in CBCL, differentiation between the aggressive subtype primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) from the generally indolent subtype PCFCL with a diffuse growth pattern is very important for therapeutic management (i.e., immuno-polychemotherapy versus local radiotherapy, respectively) and prognostic implications [27].

Regarding these diagnostic challenges, DL-based tools could potentially be used to help distinguish the different subtypes of CL. However, due to the scarcity of CL cases, especially several of the extremely rare subtypes, the validity of employing these tools in skin pathology should first be established. In contrast to CL, one of the most common, labor-intensive, and banal tasks in a dermatopathologist's practice is the detection of BCC. It is an ideal proof-of-concept topic for AI modelling in histopathology, experimented with by many groups, being a relatively straightforward binary classification task: does the slide contain BCC or not. One of the first DL approaches for automatic BCC detection achieved a balanced accuracy of 89% with a proprietary CNN architecture [29]. Since then, many groups have demonstrated the feasibility of this task using different CNN architectures, achieving very high classification AUCs [30–33], even when applied to smartphone-captured microscopic images [34,35]. Others investigated the role of DL-algorithms as a safety mechanism (i.e., second reader) to aid surgeons in the detection of BCC on Mohs micrographic surgery frozen sections [36,37]. One of the largest studies to date in terms of WSI datasets included, among a variety of computational pathology tasks, the whole-slide-level detection of BCC [38]. Utilizing a multi-country dataset of 9962 slides of neoplastic and non-neoplastic skin lesions, including 1659 BCCs, clinical-grade performance was achieved (AUC of 0.990) using a weakly supervised model trained at $5 \times$ magnification. Although the automated detection of BCC is a substantially different task than the diagnosis of CL, the preceding articles laid the foundation for the use of DL in diagnostic tasks in dermatopathology.

As the routine diagnosis of CL almost never involves a mere detection task, the distinction of two or more similar disease entities in skin biopsies is much more relevant. As such, an AI-based system accurately classified 123 of 124 (99.45%) nodular BCCs, 113 of 114 (99.4%) dermal nevi, and 123 of 123 (100%) seborrheic keratoses, in a binary classification task differentiating each common skin lesion from different 'distractors'. For example, for BCC, these included verruca vulgaris, actinic keratosis, spongiotic dermatitis, dermal nevi, and basosquamous acanthomas [39]. A simplified implementation of U-Net was used to differentiate between two intra-epidermal lesions, i.e., Bowen's disease and seborrheic keratosis, on test sets from three different institutions with high AUCs [40]. Three different deep neural networks were assessed for the classification of ten different growth patterns of BCC, including micronodular, sclerosing, and infiltrating subtypes [41].

In addition to BCCs, the distinction between benign and malignant melanocytic proliferations is a widely researched and desired task in skin pathology, and possibly represents a better approximation for the difficulty of distinguishing the different subtypes of CLs. In both skin excisions and biopsies, DL algorithms were able to classify melanoma

versus nevus [42–45]; eyelid melanoma versus benign nevus [46]; Spitz nevus versus conventional nevus [47]; benign versus malignant spitzoid neoplasms [48]; intradermal versus junctional versus compound nevi [49], and melanocytic nevi versus Spitz nevi versus invasive melanoma [50].

An important first step in the examination of skin biopsies by pathologists for the diagnosis of CL involves the assessment at low-power scanning magnification of the architecture and distribution of the lymphoid infiltrate in the superficial to deep dermis and/or subcutis, and whether there is involvement of epithelial structures, i.e., epidermis, hair follicles, and sweat glands. Since similar principles apply to the histologic appraisal of melanocytic proliferations, some studies can serve as exemplars for CL applications.

In order to address these architectural characteristics, Nofallah et al. [51] proposed a U-Net-based two-stage pipeline for the *semantic segmentation* of large skin structures including epidermis, stratum corneum, and dermis at first, followed by segmentation of melanocytic nests within the epidermis and dermis. Due to the challenging, expensive, and time-consuming task of acquiring expert-level annotations, the authors opted to use *sparse* and *coarse annotations* on small regions of WSIs. Subjective assessment of the segmentation masks revealed high-quality performance for segmenting the epidermis and dermis but lower specificity for the epidermal and dermal melanocytic nests. In a follow-up study, the segmented dermal nests were subclassified as either nevus or melanoma using three different CNN architectures. Including the segmentation masks of the epidermal and dermal melanoma nests along with the corresponding WSI improved the classification of melanocytic skin lesions compared with using the WSI alone [52]. For the envisioned application of this stepwise approach in CL, it would be relevant to first segment epidermis, dermis, subcutis, and adnexal structures, followed by segmentation of lymphocytes within these tissues. In the final step, a network could subclassify reactive and neoplastic lymphocytes, leading to a lymphoma or non-lymphoma classification.

Although there are similarities in the diagnostic approach between melanocytic lesions and CLs, there are also fundamental differences which may render the aforementioned studies less applicable for the histopathology of CLs. Both classes have characteristic architectural and cytological features; for melanoma, these include asymmetry and poor circumscription, irregular distribution of nests, pagetoid spread and ascension of melanocytes, and nuclear pleomorphism. For CTCL, these can include a band-like lymphoid infiltrate, epidermotropism, Pautrier microabscesses, and cerebriform cytomorphology. However, many of the diagnostic features for CLs show considerable overlap with common inflammatory skin diseases and systemic lymphomas with cutaneous dissemination. In addition, CLs may display a prominent tumor micro-environment, consisting of all types of white blood cells in variable amounts. This limits the applicability of approaches that use semantic segmentation of the tumoral region to obtain slide-level classifications or predictions [42,51–55].

Not surprisingly, classification tasks in the hematopathology field are more similar and more relevant for CL applications. Early work with a CNN architecture showed promising results for the classification of three subtypes of non-Hodgkin lymphoma using 374 images containing chronic lymphocytic leukemia (CLL), FL, and mantle cell lymphoma, achieving 97% accuracy [56]. Several CNNs with differing parameters were constructed for differentiating histologic images of Burkitt lymphoma (BL) from DLBCL, including several morphologic subtypes [57]. In addition, El Achi et al. evaluated DL for the classification of four different lymphoid entities using images obtained from online WSI databases, including benign lymph nodes, DLBCL, BL, and small lymphocytic lymphoma (SLL) [58]. A high accuracy was achieved for the differentiation of tumor-free lymph nodes, nodal SLL/CLL, and nodal DLBCL, using image patches extracted from representative areas in tissue microarray cores [59]. Li et al. utilized a combination of 17 CNNs for distinguishing DLBCL from non-DLBCL slides, which constituted a mixture of non-neoplastic lymph nodes as well as metastatic carcinoma

and melanoma, T-cell lymphomas, and other B-cell lymphomas, such as SLL/CLL, FL and classical Hodgkin lymphoma [60]. These studies have shown promising results for the classification of B-cell lymphomas in lymph node resection specimens and core needle biopsies using a variety of DL architectures and might represent good exemplars for the sub-classification of CBCL.

4. Identification of biomarkers for disease progression and survival

The prediction of metastatic risk and prognosis is one of the most significant future applications of AI algorithms for many cancers. For MF, there is currently a limited number of biomarkers for the prediction of disease progression and survival. In these patients, the extent of cutaneous and extracutaneous dissemination is the most important prognostic factor [26]. Additionally, large Pautrier microabscesses and dermal atypical lymphocytes in early lesions were associated with progression to advanced-stage MF [26]. Furthermore, histological large-cell transformation, defined as presence of more than 25% blast cells, was identified as an independent unfavorable prognostic factor in MF [26, 27, 61]. However, the prognostic factors in CTCL are less well-defined compared with nodal lymphomas and it remains a challenge to stratify patients according to disease progression risk [62]. Therefore, the development of AI models to predict risk of progression in patients with CTCL, by detecting novel biomarkers or combining multiple biomarkers, is of high diagnostic importance. Ideally, predictions could be made directly from routine histology, either by using known morphological features or by discovery of novel predictive features. Some studies have evaluated DL for the prediction of lymph node status and distant metastatic risk in skin carcinoma and melanoma, with variable results. Knuutila and colleagues [63] showed that ResNet-based models were able to predict whether primary cutaneous squamous cell carcinoma (SCC) would metastasize rapidly, or not metastasize at all, with an AUC of 0.747. Interestingly, including the AI prediction in a multifactorial model with conventional risk factors, such as tumor diameter ≥ 30 mm and Clark's level 5, improved the AUC to 0.917. It was concluded that the AI predictions were based on certain unknown morphological features or feature combinations. Regarding primary melanoma, Kulkarni et al. [64] proposed a combined CNN-recurrent neural network DL method to predict visceral recurrence and disease specific survival. The developed pipeline takes H&E-stained slides as input and has a 'distant metastatic recurrence' status prediction as output, achieving AUCs of 0.905 and 0.880 on two independent validation sets. It was found that the density of the lymphocyte infiltrate was an important component of the prognosis classifier. In addition, a German group aimed to predict sentinel lymph node status directly from digitized H&E slides of primary melanoma [65]. Using 415 slides from melanoma patients with known clinical outcome, the authors showed that *artificial neural networks* were able to predict lymph node status to some extent, but with too low accuracy for clinical relevance. Additionally, predictions were mostly based on factors already known from the clinical data (ulceration, tumor thickness, patient age) as opposed to independent morphological features. These three studies illustrate that it might also be possible for DL to identify known or novel morphological features in CL associated with worse prognosis. Due to the strong reliance on clinicopathological correlation in CL diagnostics, the integration of the AI prediction with clinical parameters in a multifactorial model would seem to be a very sensible approach.

In patients with PCDLBCL-LT, the presence of *CDKN2A* inactivation, *MYD88* (p.L265P) mutation, or *MYC* rearrangements, were reported to be associated with an inferior prognosis [26, 27, 66]. As these factors represent genetic abnormalities, it may be relevant to use DL for the prediction of genomic profiles of CL patients, ideally based on histopathology. This will prevent the need for assays such as Next Generation Sequencing, which might be expensive and time-consuming and require sufficient tissue. In line with PCDLBCL-LT, a combination of DL and

classical machine learning was applied to detect the presence of *MYC* rearrangements in a set of DLBCL H&E-stained slides obtained from 11 hospitals, with a sensitivity of 93% and specificity of 52% [67]. Furthermore, DL was used to predict the presence of mutated *BRAF* in WSIs of primary melanoma, achieving an AUC of 0.71 in the test set, and 0.67 on a second independent cohort. Phenotypic differences were correlated with *BRAF* status, where tumor cells with mutated *BRAF* exhibited larger and rounder nuclei [68]. In these proof-of-concept studies, although promising, the predictive values are too low for clinical use and will have to be improved with future research.

5. Identification of biomarkers for therapy response

In addition to biomarkers with prognostic value, biomarkers that can predict therapy response are highly welcomed, in line with the emergence of targeted, personalized medicine. In CTCL, tumor cells can express both programmed cell death protein 1 (PD-1) and its ligands, which encourages the use of PD-1 blockade with immune checkpoint inhibitors in patients with advanced-stage MF and Sézary syndrome [69]. However, in a phase II trial, there was an overall response rate of 38% and treatment responses did not correlate with expression of PD-L1 [70]. In addition, brentuximab vedotin is an anti-CD30 antibody-drug conjugate that is approved for treatment of patients with previously treated C-ALCL and CD30-positive MF. In a phase III trial, 56% of patients achieved an objective global response lasting at least 4 months [71]. As there is much room for improvement, AI-based biomarkers can potentially be used to predict the clinical response of CL patients to anti-PD-1 and anti-CD30 therapy as well as to novel compounds in the future.

In advanced melanoma, Hu and colleagues [72] aimed to predict the anti-PD-1 response using a CNN model based only on routine H&E-stained slides, achieving an AUC of 0.778 for correctly classifying responders and non-responders. The model generalized reasonably when applied to an independent non-small-cell lung cancer cohort. Additionally, Johannet et al. [53] built a multivariable classifier to predict immune checkpoint inhibitor treatment outcome in metastatic melanoma based on integrated WSI and patient clinicodemographic variables. A segmentation network was trained to distinguish tumor, lymphocyte, and connective tissue compartments in lymph nodes and subcutaneous tissue with robust accuracy. A response classifier, trained on tumor tiles, subsequently predicted either response to immunotherapy or progression of disease, apparently based on the density and size of nuclei. Merging the response classifier with the patient's Eastern Cooperative Oncology Group performance status and treatment regimen further improved the prediction accuracy and the resulting multivariable classifier accurately stratified patients into high versus low-risk groups for disease progression. These studies demonstrated that AI, using information obtained from routine H&E-slides, with or without integration of patient variables, may also be a potential tool for the prediction therapy response in CL patients.

6. Quantification of established biomarkers

Next to AI as detector of novel biomarkers, AI can also help to improve quantification of established biomarkers. In MF, both CD30 and Ki-67 expression are associated with worse survival in patients with skin tumors (T3 disease) [61, 73]. However, scoring of these immunohistochemical stains is subject to arbitrary cut-off values and high interobserver variability between pathologists. Therefore, it would be beneficial to have DL-models for standardized quantification of these biomarkers. In lymph node metastases of melanoma, Alheejawi [74] published a CNN-based approach for the automated calculation of the proliferation index based on the Ki-67 immunohistochemical stain. The melanoma regions were identified using a Melan A/MART1-stained image and superimposed on a Ki-67-stained consecutive section. This is followed by the segmentation and classification of active and passive

nuclei by a CNN architecture to calculate the proliferation index. Although illustrative, the quantification of biomarkers in CLs will be more challenging as it is more difficult to segment the neoplastic cells in most cases.

7. Challenges for deep learning in cutaneous lymphoma

In this review we have covered a large number of studies regarding AI in the pathology of skin cancer and systemic lymphoma which might be useful for CL applications. Although high performances are reported for a multitude of DL tasks, in many of the discussed studies in this review, we have recognized important limitations. Since nearly all covered research concerns feasibility studies, the application in clinical practice is largely speculative. Additionally, we believe there are several specific challenges for the application of DL in histopathology of CL.

Firstly, all of the mentioned studies have retrospective designs, where a prospective design would be needed to confirm the clinical impact of DL-based models. Secondly, many studies have small and/or unbalanced datasets and are based on WSIs from a single institution, lacking external validation. These facts make it difficult to generalize the model's performance, which would probably show lower performance on datasets from other institutes or countries with different operating procedures. Therefore, collaborations between pathology institutions for sharing WSI datasets should be encouraged to increase the size of the datasets as well as to overcome inter-institutional and/or inter-regional variation. Publicly accessible WSI repositories can be utilized for teaching and research purposes, as well as provide diagnostic references in routine diagnostics. These datasets also provide the opportunity to assemble a diverse set of cases of rare CLs from different laboratories all over the world that can be used to train AI models and increase the generalizability for different scanners and laboratory procedures. In addition, international, multi-center datasets might overcome challenges in geographical differences that may exist for certain CL entities and mimics. As an example, a histopathology dataset for the training of machine learning models for skin cancer was made available in 2021, containing 290 high-resolution images with associated hand-annotated segmentation masks for 12 tissue classes, including among others epidermis, dermis, hair follicle, and glands, as well as BCC and SCC annotations [75]. The Cancer Genome Atlas (TCGA) repository [76] hosts a multitude of annotated pathological slides of different cancers, including melanoma and DLBCL, but unfortunately lacks CL slides. Currently, there are several online slide libraries, hosting multiple H&E-stained cases of CTCL and CBCL, with a variable amount of accompanying clinical information, immunostains, as well as 'control' tissues in the form of cutaneous pseudolymphomas and BIDs. These WSIs can often be viewed in either the web browser or using certain desktop software. An overview of the publicly available WSI repositories containing CL cases is shown in [Supplementary Table 3](#). Possibly, a contribution can be made by Generative Adversarial Networks by generating synthetic image samples of CL [77]. For both clinicians and researchers, we endorse the establishment of public WSI repositories, especially for rare diseases, such as CL.

In addition to the limitations mentioned above, many of the proposed algorithms have limited applicability in clinical practice by neglecting the emulation of a real-world environment [78]. Most of the discussed studies have designed a binary classification algorithm, whereas in clinical reality pathologists have to differentiate a broad spectrum of diagnoses. Complementary to this, using only unequivocal cases [50] or artifact-free WSIs in the dataset artificially simplifies the task. Studies often used a region of interest (ROI)-level or patch-level classification approach, where a pathologist has already selected the most appropriate areas to be classified. These studies did not provide a final slide-level classification or performance evaluation and/or validation in WSIs, which does not mimic a real-world scenario of a pathologist's workflow. From the discussed studies, only a minority provided insights into whole slide-level diagnostic performance for both

skin cancer [25,38,39,42,48] and lymph node cancer [23]. To improve the clinical reliability, colleagues at the Technical University Berlin emphasized the benefits of the visualization of a model's decision process. For the detection of three tumor entities including cutaneous melanoma, they also demonstrated that latent biases in datasets could be uncovered with the use of so-called explanation heatmaps [79].

Regarding ROIs, some algorithms only used tiles from manually annotated regions [46,50,80] or from randomly cropped areas of the WSI [44,45] as input data. The localization of tumor areas in sections of epithelial and melanocytic tumors, and certain high-grade or transformed lymphomas, can usually be demarcated as a ROI. However, in many cases of CL, there is a variegated mix of neoplastic and reactive infiltrates with intimate relationships with epithelial structures. This fact makes it difficult, and undesirable, to specifically annotate tumoral regions and renders these approaches not feasible for most forms of CL. Therefore, weakly supervised learning methods, which only require a slide-level diagnosis without tumor annotations, are probably more appropriate for DL applications in CL. Weakly supervised DL has been used for the detection of BCC [32,38] and for the differentiation of early MF and BIDs [19]. Alternatively, we envision a *supervised learning* approach incorporating the segmentation of different skin structures with the segmentation of neoplastic and reactive lymphocytes within these structures on a whole-slide level.

Remarkably, in most of the discussed DP studies, there is a noticeable lack of incorporation or consideration of clinical context. It is very well conceivable that an AI model cannot distinguish CLs on the basis of H&E-stained slides alone without the addition of some form of clinical data, photographs, or immunohistochemical assays. Therefore, we believe future studies in DP of CL will benefit from multi-modal models integrating the aforementioned data modalities to achieve better performance compared with models based solely on H&E-stained images. The integration of patient data was already shown to improve the classification accuracy of skin cancer in low-confidence AI predictions [80].

Another important limiting factor is the imperfect nature of ground-truth labels that are used for model training and testing, in part caused by high dermatopathologist interobserver discordance. This is pertinent for ambiguous lesions, such as many melanocytic tumors, but also will be especially relevant for several subtypes of CL. Interobserver variation for the histopathologic diagnosis of MF has been reported in about ~20% of cases [3]. Some studies were well aware of this fact. For example, melanocytic lesions were only included in the study set if consensus was reached by three dermatopathologists [24] or by a minimum of two board-certified pathologists [46]. Some authors highlighted the importance of involvement of the pathologist for manual curation of the dataset to optimize the model's performance [47]. In CL, we strongly suggest that only consensus-based diagnoses by an expert panel, considered to be the gold standard, are used for ground-truth labelling to improve reliability and performance of the DL-models.

8. Conclusions

Currently, AI in pathology of CL is just starting up. Therefore, this review aimed to provide a comprehensive overview of DL studies in other skin cancers and systemic lymphomas, which might be adapted in the future for CL applications, or serve as good proof-of-concepts for this purpose. There are many approaches that could yield promising results in a variety of tasks, although many studies are limited by the employed methods and several specific challenges exist for DL tasks in pathology of CL. Nevertheless, we anticipate that AI applications in CL pathology will rapidly increase in the near future.

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Thom Doeleman: Writing – original draft, Conceptualization. **Liesbeth Hondelink:** Writing – original draft, Writing – review & editing. **Maarten Vermeer:** Writing – review & editing. **Marijke van Dijk:** Writing – review & editing. **Jesper Kers:** Writing – review & editing. **Anne Schrader:** Conceptualization, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Data Availability

No data was used for the research described in the article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semcancer.2023.06.004.

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