The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathological reporting of primary cutaneous lymphoma

April 2022

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Unique document number	G190
Document name	Dataset for histopathological reporting of primary cutaneous lymphoma
Version number	1
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Date active	April 2023 **(to be implemented within 3 months)**
Date for full review	April 2026
Comments	In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 6 December 2022 to 3 January 2023. Responses and authors' comments are available to view, following final publication of this dataset. **Dr Brian Rous** **Clinical Lead for Guideline Review**

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Registered charity in England and Wales, no. 261035

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Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices E and F) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- British Association of Dermatologists
- British Society for Dermatopathology
- National Specialist Dermatopathology External Quality Assessment (NSDEQA) scheme
- British Lymphoma Pathology Group
- UK Cutaneous Lymphoma Group.

The information used to develop this dataset was obtained by undertaking a systematic search of the PubMed database, existing NICE, UK and international guidance, the 2018 edition of the World Health Organization (WHO) Classification of Skin Tumours and the 2017 edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.[1–5] Key terms searched included ‘cutaneous lymphoma’, ‘clonality’, ‘cutaneous lymphoma staging’ and ‘mycosis fungoides staging’ and dates searched were between November 2019 and September 2022. Twenty-six studies met the selection criteria and were considered for review. Published evidence was evaluated using modified SIGN guidance (see Appendix G). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset. The majority of the workup for cutaneous lymphoma can be done at a local level. Where necessary, samples for molecular studies can be referred to specialised centres that have the equipment to perform these tests.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and the Specialty Advisory Committee on Dermatopathology; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed

changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group, and was placed on the College website for consultation with the membership from 6 December 2022 to 3 January 2023. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The authors have no conflicts of interest to declare.

1 Introduction

Primary cutaneous lymphoma encompasses a heterogenous group of extranodal non-Hodgkin lymphomas, which include cutaneous T-cell lymphoma (CTCL), cutaneous B-cell lymphoma (CBCL) and NK cell lymphomas. Primary cutaneous lymphomas have been defined by the European Organisation for Research and Treatment of Cancer (EORTC) – WHO classification and incorporated into the WHO Classification of Skin Tumours and the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.[1–4] Provisional entities include poorly defined lymphomas for which there is not enough evidence to define a distinctive entity and also entities for which it is not entirely clear from available evidence if the disease is reactive or truly neoplastic. The classification of primary skin lymphomas in both publications is almost identical except for a few small differences. We have included the WHO Classification of Skin Tumours in Appendix A.

In industrialised countries, primary cutaneous lymphoma comprise approximately 75–80% CTCL and 20–25% CBCL.[6] Mycosis fungoides (MF) represents the commonest subtype of CTCL (60% of CTCLs and approximately 50% of all primary cutaneous lymphomas) followed by the CD30-positive lymphoproliferative disorders (about 25% of all CTCLs).[1,6] A UK National Cancer Information Network audit of newly diagnosed cases of CTCL from 2009 to 2013 found an annual incidence of 0.7 per 100,000 UK population.[7]

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists, dermatopathologists, skin multidisciplinary teams (MDTs), cutaneous lymphoma MDTs and, on their behalf, the suppliers of IT products to laboratories. The secondary users are cancer registries, biomedical scientists and clinicians in secondary and primary care within the NHS.

This is the first dataset for histopathological reporting of primary cutaneous lymphoma. Datasets in general provide a standardised cancer reporting framework and guide patient management as part of an MDT meeting, which both reduce the risk of histological misdiagnosis and help to ensure that clinicians have all the relevant pathological information required for tumour typing, staging, management and prognosis. They also facilitate audit and research.

As the title suggests, this dataset does not cover cutaneous involvement by systemic lymphoma. As there is significant overlap in the reporting of systemic lymphomas and primary cutaneous lymphomas, information from the *Standards for Specialist Laboratory Integration* and *Dataset for Histopathological Reporting of Lymphomas*[8] has been included in this dataset, where applicable, with the permission of the authors.

1.2 Variation from the past standard dataset model for reporting solid cancers

With the advancement of molecular pathology, many aspects involved in the diagnosis of lymphoma, and indeed increasing numbers of solid cancers, have changed in recent years. This means cutaneous lymphoma diagnosis does not suit the past standard model adopted for the RCPath cancer datasets, which encompassed a range of solid cancers, and requires a considerably different approach.

Firstly, haematoxylin and eosin (H&E)-stained sections are only the starting point for histological assessment of suspected cutaneous lymphoma, with a panel of immunohistochemical stains used routinely as an essential component of the diagnostic process. Often the diagnosis of cutaneous lymphoma requires haematological and molecular genetic data, which are not all generated in the cellular pathology laboratory. All of this information should be taken into consideration and a single component (e.g. polymerase chain reaction [PCR] clonality results) should be interpreted in the context of everything else including very close clinicopathological correlation, which is particularly important in the diagnosis of cutaneous lymphoma, due to the differential diagnoses with inflammatory conditions and systemic lymphoproliferative disorders. It is important to highlight that the diagnosis of cutaneous lymphoma, in particular MF, can be very difficult, and often multiple biopsies from different cutaneous sites and taken during variable periods of time are necessary to confirm the diagnosis. When evaluating a biopsy for cutaneous lymphoma, it is crucial to assess whether previous biopsies have been performed and, if this is the case, these biopsies should be reviewed and the findings integrated in the final report.

1.3 Who reports cutaneous lymphomas

Cutaneous lymphomas should be reported by dermatopathologists or haematopathologists with sufficient experience and diagnostic exposure to such samples, in an appropriate supporting specialist setup and in close collaboration with dermatologists managing the patient's care. In the case of paediatric cutaneous lymphomas, the input of paediatric pathologists is also important. Regardless of whether they are a dermatopathologist or haematopathologist, it is essential that they have a good general understanding of the pathology of lymphoproliferations and knowledge of the overlapping inflammatory skin conditions. They must be local/regional specialised skin or regional/network haemato-oncology MDT members and part of a NICE cutaneous lymphoma specialist supra-regional network MDT.[9] The UK supra-regional network model provides an option for colleagues who cannot establish a diagnosis locally or regionally.

Across the country there are different specialist setups reporting cutaneous lymphomas: haematopathologists working in Haematological Malignancy Diagnostic Service (HMDS) centres, and dermatopathologists with appropriate subspecialist training working in large centres with cutaneous pathology expertise. A degree of centralisation for the reviewing of cutaneous lymphomas is required as some of the entities are very rare and it is therefore difficult to gain sufficient diagnostic exposure and experience elsewhere.

It is acknowledged that both dermatopathologists and haematopathologists provide a slightly different, but equally valuable, viewpoint when reporting cases of suspected cutaneous lymphoma, and in some instances, it may be appropriate to report a case together. For example, when an inflammatory skin condition is considered in the differential diagnosis, a haematopathologist may ask for a dermatopathologist's opinion and the converse is likely to occur when a systemic lymphoma enters the differential diagnosis.

It is, however, important to highlight that not all pathologists who are likely to come across cases of suspected cutaneous lymphoma will be working in a regional/supra-regional cutaneous lymphoma centre. These pathologists play an important role in facilitating provisional diagnosis and managing referral to specialist regional services.

2 Clinical information required on the specimen request form

Provision of clinical information is the responsibility of the clinician submitting a specimen for pathological examination. Primary cutaneous lymphomas are relatively rare diseases that can be challenging to diagnose and treat and therefore require specialist input. This means that it is particularly important that adequate clinical information is provided as this is usually included in the report sent to the specialist MDT +/- supra-network MDT (Appendix E).

3 Preparation of specimens before dissection and frozen sampling

The standard fixative enabling high-quality immunohistochemistry and genetic investigation is neutral buffered formalin. A consistent fixation time of approximately 24 hours aids uniform tissue preservation and reproducibility in immunostaining.

Ideally, if there is a strong clinical suspicion of lymphoma it is recommended that fresh tissue be obtained for molecular testing. However, the priority is to obtain formalin-fixed tissue for morphological assessment and immunohistochemistry. TCR/IG gene analysis can be performed with less sensitivity in formalin-fixed paraffin embedded material.

Following a diagnosis of MF or Sezary syndrome (SS), flow cytometry should be performed on peripheral blood to identify and/or quantify the Sezary cells.[10] Absolute values of CD4+CD26- or of CD4+CD7- determined by flow cytometry are used to determine blood classification from B0-2 in MF/SS where B0 < 250 IU, B1 = 250 ≤ 1000 IU and B2 ≥ 1000 IU and have replaced the use of manual Sezary counts.[11]

4 Specimen handling, dissection and block selection

The specimen should be measured in three dimensions (millimetres), the whole of the sample should be referred for histological examination and inking is not required. The presence, absence or any uncertainty about the existence of a lesion or abnormality to the naked eye must be recorded. When a lesion is apparent, it should be measured.

5 Core data items

As stated by the dataset for histopathological reporting of lymphomas, each lymphoma entity as specified by the WHO classification is defined by a combination of features including clinical context, morphology, immunophenotype and genotype (including clonality where appropriate). In addition to definitive diagnosis, these represent in principle a core of items that must be included in pathology reports. Depending on the lymphoma entity, emphasis varies. Diagnosis of all entities requires careful assessment of morphology and immunophenotyping. For some, the clinical setting is crucially important. In other entities, presence of specific genetic markers and assessment of clonality are essential for diagnosis.

5.1 Clinical data

The site of origin and type of specimen are core clinical items for the pathology report. As per the specimen request form, clinical history is required and, in some cases, essential for correct diagnosis. The provision of clinical photographs can be diagnostically helpful for clinicopathological correlation and therefore improve diagnostic accuracy.

[Level of evidence D – Clinical photographs are frequently used for clinicopathological correlation and can help in the diagnosis of cutaneous lymphomas.]

5.2 Pathological data

- WHO lymphoma entity.
- Clinicopathological correlation.
- Morphology.
- Immunophenotype and Epstein–Barr virus (EBV)-encoded RNA (EBER) status.
- Genotype, including clonality where appropriate (see section 5.2.5).

Appendix A contains a list of essential investigations to be undertaken for the diagnosis of individual lymphomas. The results of these essential investigations for the individual entities represent the mandatory core information to be included in the report. We have also included additional investigations as non-core items.

5.2.1 WHO lymphoma entity

Lymphomas should be categorised according to the WHO classification.[3,4]

Definitive pathological diagnosis cannot always be reached and in these cases diagnostic uncertainty should be clearly expressed. The MDT can be used in such circumstances as the appropriate forum for dialogue to achieve a pragmatic consensus to guide clinical management, acknowledging and taking mutual responsibility for any risk involved. Further biopsy/biopsies may be the most appropriate course of action.

The reason for diagnostic uncertainty should be specified as it may guide further management. Reasons include:

- limited sample quantity (e.g. too superficial biopsy for confident diagnosis of subcutaneous panniculitis-like T-cell lymphoma)
- limited sample quality (e.g. crush artefact impairs morphological assessment)
- complexity of histological interpretation (e.g. morphological features that are subtle or not entirely typical of an entity)
- contradiction between results of component tests contributing to diagnosis (e.g. unexpected combinations of immunohistochemistry results; TCR/IG analysis not supporting morphological assessment)
- contradiction between clinical context and histological features
- difference of opinion between appropriately skilled individuals assessing the case (e.g. failure to achieve consensus during double reporting).

5.2.2 Clinicopathological correlation

Clinicopathological correlation is an essential component contributing to the diagnosis of a specific cutaneous lymphoma entity as defined by the WHO classification. Aspects of the clinical setting that can affect the diagnosis are age, duration of the disease, drug history, clinical appearance, site and number of skin lesion(s), extracutaneous involvement and immunosuppression. For example, the clinical appearance may be described as single or multiple lesions that are patch(es), plaque(s), tumour(s) or erythroderma +/- ulceration. Clinical photographs are usually very helpful. In the context of MF, whole skin and nodal examination is often more informative for staging purposes while photographs alone can be unreliable and lead to misinterpretation. Clinicians and pathologists must be aware of the need for comprehensive clinical information.

For some entities pathological investigations alone cannot provide definitive diagnosis outside the appropriate clinical context. For example, the differential diagnosis for a CD30-positive

lymphoproliferative disorder includes reactive conditions, lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma, cutaneous involvement by systemic anaplastic large cell lymphoma and transformed MF. Only clinicopathological correlation can enable definitive diagnosis and this should be stated in the report.

In the clinical scenario of a single lesion, a florid reactive lymphoid infiltrate (pseudolymphoma) is usually higher compared to when there are multiple lesions. Caution should be taken when interpreting such lesions to avoid overdiagnosis of lymphoma. This scenario exemplifies the value and utility of clinical photographs. In addition, providing clinical information as to whether the patient has a single lesion macroscopically (unifocal) or multiple lesions (multifocal), the size of the lesion and the presence or absence of regression is therefore important.

[Level of evidence A – Clinicopathological correlation is an essential component contributing to specific diagnosis of a WHO lymphoma entity.][12]

5.2.3 Morphology

Morphological interpretation is paramount in the diagnosis of cutaneous lymphoma and provides the basis for a differential diagnosis and subsequent further tests. A morphological description is required in all cases. The localisation of the infiltrate whether epidermotropic, dermal and or subcutaneous is very important as is the presence and absence of folliculotropis, syringotropism and angiocentricity.

The presence and extent of folliculotropism and the presence or absence of large cell transformation is important in the context of MF due to their prognostic relevance.

[Level of evidence A – Lymphoma entities are characterised by typical histomorphological features.][13]

5.2.4 Immunophenotype

In addition to morphology, cutaneous lymphoma entities are defined by specific immunophenotypes obtained by immunohistochemistry. Characteristic immunophenotypes are outlined in both the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* and *WHO Classification of Skin Tumours*.[3,4] Some cutaneous lymphomas are characterised by expression of distinctive and unique markers that are essential for diagnosis. These are listed in Appendix A. The immunohistochemical profile should be interpreted in the context of the clinical, morphological and molecular test findings. Among the morphological considerations, it is important to correctly interpret the presence of non-neoplastic lymphoid cells admixed with potential lymphoma components. This is more often a source of difficulty in skin infiltrates than in diagnostic lymph nodes. It needs careful consideration in composing reports clearly so that the immunophenotype of candidate neoplastic cells is clearly described separately from the reactive background, recording proportions of CD4-positive and CD8-positive cells, for example, and noting CD20 expression limited to reactive B-lymphocytes in the context of a cutaneous small T-cell proliferation. Diagnostic immunohistochemistry panels as part of the core and non-core data are provided in Appendix A.

Immunohistochemistry is not only required for diagnosis but can also be important for prognostication and treatment guidance. For example, determining the presence and approximate percentage of CD30-positive tumour cells is necessary for treatment decisions regarding brentuximab in the management of primary CD30-positive cutaneous lymphomas.

Immunohistochemistry requires good technique and careful interpretation, with the use of appropriate controls and participation in an accredited external quality assurance (EQA) scheme. Laboratory staff must be fully aware of the staining characteristics of all antibodies employed (e.g. nuclear versus cytoplasmic) and the technical requirements for each antibody.

[Level of evidence A – Immunophenotype is an essential component contributing to specific diagnosis of a WHO lymphoma entity.]

5.2.5 Epstein–Barr virus status

In addition to morphology and immunohistochemistry, EBV testing by in-situ hybridisation is important in the diagnosis of a small number of cutaneous lymphomas.

In-situ hybridisation requires good technique and careful interpretation, with the use of appropriate controls and participation in an accredited EQA scheme. Laboratory staff must be fully aware of the staining characteristics of all antibodies employed (e.g. nuclear versus cytoplasmic) and the technical requirements for each antibody.

[Level of evidence A – EBV status is an essential component contributing to specific diagnosis of some WHO lymphoma entities e.g. EBV-positive mucocutaneous ulcer.]

5.2.6 Clonality

Lymphoproliferative disorders involving the skin can be diagnostically challenging given the significant clinical and histological overlap with benign inflammatory dermatoses containing reactive lymphoid infiltrates. There are inherent limitations in the diagnostic sensitivity and specificity of morphology and immunophenotype to reliably distinguish between some lymphoproliferative disorders and benign inflammatory dermatoses.[14] Clonality studies of the immunoglobulin and T-cell receptor genes by PCR or next generation sequencing (NGS) can therefore be very useful in the assessment of cutaneous lymphoid infiltrates suspicious for lymphoma. Indeed, clonality testing historically has been used more frequently in this setting than in the assessment of lymphoid populations in lymph nodes or other tissue. With the adoption of the National Genomic Test Directory for Cancer the use of clonality studies in the setting of cutaneous and systemic lymphomas it more widely used.

It should be noted, however, that clonality assays are not always appropriate, have their limitations and may lead to diagnostic confusion if used inappropriately.

Some limitations of clonality assays are:

- early manifestations of cutaneous lymphomas, especially CTCL, or samples with a low level of disease involvement can be particularly difficult to differentiate from inflammatory conditions. For instance, only 64.4% of early-stage lesions of MF may demonstrate T-cell clonality.[15] This may be due to the accompanying reactive lymphoid infiltrate sometimes impairing the detection of the clonal atypical lymphocytic population and therefore leading to false negatives. The present assays require the specimen to contain greater than 5% clonal T cells to demonstrate a clonal TCR gene rearrangement, although emerging use of NGS platforms may be more sensitive.[16–19]
- a successful test relies on good quality DNA. DNA extracted from formalin-fixed paraffin-embedded tissue is sometimes of moderate to poor quality due to formalin causing degradation of nucleic acids and it may contain PCR inhibitors leading to false negatives or test failure.[20] Use of buffered formalin limits the chance of technical failure.
- occasionally a reactive lymphoid population is clonal resulting in false positives. This highlights the importance of judicious testing and careful interpretation in the context of the other pathological and clinical findings by an experienced user.
- the presence of an identical clone in two distant skin lesions is highly suspicious for lymphoma, however polyclonality does not exclude lymphoma
- investigated T-cell populations show increasing numbers of restricted/oligoclonal or clonal bands with advancing age (particularly over 50 years), leading to false positive results in the older population.

A study performed in the USA developed appropriate use criteria in dermatopathology by combining the best scientific evidence available with the collective judgement of experts to yield a statement of the appropriateness for performing a clonality assay in specific clinical

scenarios encountered in everyday practice.[21,22] Summary tables of this guidance are included in Appendix D. Please note this is for assistance only and is not expected to be used as strict criteria.

Clonality testing, in the appropriate clinical setting, is not always necessary for diagnosis. However, if organisational and financial circumstances allow, it is good practice to conduct it for selected, ambiguous cases of MF and primarily use the result as a benchmark for comparison with further biopsies and for the assessment of lymph node and blood involvement.

TCR/IG gene analysis results are meaningful only when interpreted by an experienced user and in the context of the clinical, morphological and immunophenotypical findings.[23] In our view, the current situation in the UK where PCR clonality results in isolation are sometimes available to a number of clinical profiles, such as dermatologists, can be highly confusing and potentially dangerous. We feel that clonality results should be conveyed in an integrated pathology report and never reported in isolation. TCR/IG gene analysis requires specialist staff, careful interpretation and participation in an accredited EQA scheme and the tests are included in the National Health Service England (NHSE) cancer core test directory.[24] All laboratories in the UK undertaking lymphoid clonality studies by PCR use the Biomed-2 sets of PCR primers. Guidance on interpretation is available in the most recent EuroClonality report.[25]

[Level of evidence B – Evidence of clonality is by PCR is evidence of lymphoid neoplasia and is essential for diagnosis of some of the WHO lymphoma entities.]

5.2.7 Genotype

Genetic investigations are not routinely performed in all cases of suspected cutaneous lymphoma but may be required in cases where molecular assessment will aid diagnosis or management (Appendix D). The NHSE National Genomic Test Directory for Cancer specifies the genomic tests commissioned by the NHS in England for cancer (including lymphoma), the technology by which they are available and the patients who will be eligible to access a test. These tests are delivered by the seven national genomic laboratory hubs.[24]

For example, fluorescence in-situ hybridisation (FISH) analysis frequently shows translocations involving MYC, BCL2 or BCL6, and IGH genes in primary cutaneous large B-cell lymphoma, leg type, unlike diffuse follicle centre lymphoma, which may be in the differential diagnosis.[26] Although not a universally held view, some contributors to this dataset feel all potential cases of cutaneous diffuse large B-cell lymphoma or otherwise looking like high-grade B-cell lymphomas in the skin should be consistently tested by FISH for MYC, BCL2 and BCL6 translocations.[27] The same view is held regarding FISH testing for BCL2 gene rearrangement in suspected cases of primary cutaneous follicle centre lymphoma. This helps to identify the outliers that are not primary cutaneous, which may not yet be evident clinically.

FISH analysis can also highlight rearrangements involving the *DUSP22-IRF4* locus on chromosome 6p25.3 in approximately 25% of primary cutaneous anaplastic large cell lymphoma cases and in a minority (<5%) of lymphomatoid papulosis cases.[28,29] Indeed, some contributors to this dataset feel that DUSP22 and P63 should be part of the routine FISH testing for primary cutaneous anaplastic large cell lymphoma in view of the prognostic associations.[30]

Another example is in the context of angioimmunoblastic T-cell lymphoma, which is underdiagnosed in skin biopsies and may be confusing as a range of cutaneous lymphomas can show variable expression of follicular T-helper markers. This is important to highlight as skin changes may considerably precede systemic manifestations in angioimmunoblastic T-cell lymphoma. We think that, in difficult cases when clinical circumstances are not particularly helpful, the only way to reliably sort out cases from angioimmunoblastic T-cell lymphoma at the point of biopsy is mutation testing for TET2, IDH2, DNMT3 and RHOA genes. This should lead to less missed diagnoses of angioimmunoblastic T-cell lymphoma in skin biopsies.

Genetic tests such as FISH require good technique, specialist staff, careful interpretation in the context of the clinical and histological findings, and participation in accredited EQA schemes. Newer platforms to analyse rearrangements and translocations are emerging with the NHSE commissioning of national molecular diagnostics for cancers including lymphoma.

[Level of evidence A – Lymphoma entities are characterised by specific genetic markers.]

6 Non-core data items

A range of immunophenotypic and genetic features that may aid diagnosis and provide additional prognostic information may be assessed in individual circumstances. Additional investigations, useful but not essential for diagnosis, are highlighted in Appendix A.

7 Diagnostic coding and staging

International Classification of Diseases for Oncology (ICD-O)-3 codes with the corresponding lymphoma entities as listed in the WHO skin classification are detailed in Appendix A. The SNOMED-CT morphology (M) codes are provided in Appendix C. Most laboratory reporting systems are now adopting the use of SNOMED-CT and these codes should be used consistently for definitive diagnostic coding of lymphomas in reports. SNOMED topography (T) codes in standard use should be used in conjunction.

8 Reporting of small biopsy specimens

Reporting of small biopsy specimens follows the same principles for other biopsy material taken for lymphoma diagnosis. Pathologists should be mindful of diagnostic limitations of small biopsies, in particular the limited scope for immunohistochemistry and PCR. When a small sample is received, a slide with sections stained with H&E is obtained and based on the findings a basic immunohistochemical panel is requested to try and reach a specific diagnosis. If any tissue remains, a wider immunohistochemical panel and if possible clonality studies are requested.

9 Reporting of frozen sections

The diagnosis of primary cutaneous lymphoma in the UK never intends to involve frozen section assessment. In rare and unexpected circumstances, if lymphoma is considered as the diagnosis on frozen section analysis, pathologists should be aware that establishing a definitive diagnosis is not possible without additional studies.

10 Criteria for audit

As recommended by the RCPath as key assurance indicators (see Key Assurance Indicators for Pathology Services, November 2019) and key performance indicators (see Key Performance Indicators – Proposals for implementation, July 2013):

- cutaneous lymphoma biopsies must be reported using a template or proforma, including items listed in the English COSD which are, by definition, core data items in RCPath cancer datasets. NHS Trusts are required to implement the structured recording of core pathology data in the COSD.
  - standard: 95% of reports must contain structured data

- histopathology cases that are reported, confirmed and authorised within seven and ten calendar days of the procedure
    - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

Note: The latter refers to reports that are completed with the use of sections stained with H&E and immunohistochemistry. FISH and NGS are not commonly used in the diagnosis of cutaneous lymphomas. In cases when these complementary studies are used, it should be highlighted in the report that a supplementary report will be issued when the results become available.

11 Acknowledgements

We would like to thank the authors of the lymphoma dataset, Professor Stefan Dojcinov, Dr Bridget Wilkins and Professor Maria Calaminici, for providing a framework for this dataset and their significant contribution to the content.

We would also like to thank Professor Sean Whittaker and Professor Julia Scarisbrick who are consultant dermatologists with specialist expertise in cutaneous lymphoma and provided valuable insights into the management of patients with primary cutaneous lymphoma.

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Appendix A WHO classification of primary cutaneous lymphomas with ICD-O-3 codes, core and non-core diagnostic requirements

Description of histomorphology and interrogation of immunophenotype are essential core data items for the diagnosis of all WHO cutaneous lymphoma classification entities. Many of the entities, in addition to broad phenotypic characterisation, require interrogation of small numbers of immunohistochemical markers that are entity specific or provide important prognostic information. The column headed 'Core data' indicates the minimum number of tests required upon which a safe diagnosis can be achieved in the majority of cases, when evaluated in the context of adequate clinical information. The 'Non-core data' column highlights immunohistochemical and genetic markers that provide additional useful diagnostic or prognostic information that is not considered mandatory or is not essential for management decisions.

Please note clinical context is a core data item for all cutaneous lymphomas.

This does not comprehensively cover the immunohistochemistry panels and molecular data required to distinguish the following entities from certain systemic lymphomas, which may be in the differential diagnosis.

(*) Items usually not interrogated on tissue sections.

(**) Two cytotoxic markers are adequate.

WHO 2018 Classification of Skin Tumours

	ICD-O-3	Core data	Non-core data
Mycosis fungoides	9700/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30	T-cell clonality, αβ, ki-67
Sezary syndrome	9701/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30 Flow cytometry*	T-cell clonality, αβ, ki-67
Lymphomatoid papulosis	9718/1	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, Granzyme B, TIA1, Perforin,** CD25	ki-67, FISH for DUSP22-IRF4 rearrangement
Primary cutaneous anaplastic large cell lymphoma	9718/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, Granzyme B, TIA1, Perforin,** CD25, ALK1	ki-67, CD15, EMA, T-cell clonality FISH for DUSP22 and P63
Cutaneous adult T-cell leukaemia/lymphoma	9827/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25	ki-67, Granzyme B, TIA1, Perforin, FOXP3, T-cell clonality
Subcutaneous panniculitis-like T-cell lymphoma	9708/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, αβ, γδ, CD56, EBER(ISH), Granzyme B, TIA1, Perforin**	CD123, ki-67, T-cell clonality
Hydroa vacciniforme-like lymphoproliferative disorder	9725/1	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, EBER(ISH), CD56, αβ, γδ, Granzyme B, TIA1, Perforin	
Extranodal NK/T-cell lymphoma, nasal type	9719/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD56,	ki-67, CD25, αβ, T-cell clonality

		Granzyme B, TIA1, Perforin,** EBER(ISH)	
Primary cutaneous gamma-delta T-cell lymphoma	9726/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD56, Granzyme B, TIA1, Perforin,** γδ, EBER(ISH)	ki-67, αβ, T-cell clonality
Primary cutaneous CD8+ aggressive epidermotrophic cytotoxic T-cell lymphoma	9709/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, Granzyme B, TIA1, Perforin**	ki-67, αβ, γδ, CD56, CD25, T-cell clonality
Primary cutaneous acral CD8+ T-cell lymphoma	9709/3	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, TIA1	αβ, ki-67, CD56, CD25, T-cell clonality
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	9709/1	CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, PD1, ICOS, BCL-6, CXCL13, CD21, CD10, EBER(ISH)	ki-67, T-cell clonality
Primary cutaneous marginal zone lymphoma	9699/3	CD20, CD3, BCL-2, CD5, CD10, BCL-6, cyclin-D1, CD21, CD23, light chains (IHC or ISH), IgM, IgD, IgG, IgA, ki-67, B-cell clonality by PCR	CD79a, CD123
Primary cutaneous follicle centre lymphoma	9597/3	CD20, CD3, BCL-2, CD5, CD10, BCL-6, cyclin-D1, CD21, CD23, ki-67, light chains	CD79a, MUM-1, B-cell clonality, FISH for BCL2 rearrangement
Primary cutaneous diffuse large B-cell lymphoma, leg type	9680/3	CD20, CD3, BCL-2, CD10, BCL-6, CD21, MUM-1, CD23, ki-67, MYC (IHC), cyclin D1, EBER(ISH)	CD30, CD25, FISH for MYC rearrangement (if rearranged proceed to investigate BCL2/6 rearrangements)
EBV-positive mucocutaneous ulcer	9680/1	CD20, CD3, PAX-5, CD30, EBER(ISH), ki-67, CD5, CD15, MUM-1	OCT2, CD10, BCL-6
Lymphomatoid granulomatosis, grade 1-2	9766/1	CD20, CD3, CD30, EBER(ISH), MUM-1, BCL-2, BCL-6, CD10, ki-67	
Lymphomatoid granulomatosis, grade 3	9766/3	CD20, CD3, CD30, EBER(ISH), MUM-1, BCL-2, BCL-6, CD10, ki-67, MYC	
Blastic plasmacytoid dendritic cell neoplasm	9727/3	CD20, CD2, CD3, CD4, CD56, CD123, CD30, ki-67, CD5, EBER(ISH), CD8, TIA1, CD34, CD33, MPO, CD117, TdT, PAX5	BCL-2
Mast cell sarcoma	9740/3	CD117 (or other mast cell markers e.g. tryptase), CD25, CD2, CD3, CD20	CD30, ki-67

Indolent systemic mastocytosis	9741/1	CD117 (or other mast cell markers e.g. tryptase)	CD25, CD2, CD30, ki-67
Aggressive systemic mastocytosis	9741/3	CD117 (or other mast cell markers e.g. tryptase)	CD25, CD2, CD30, ki-67
Systemic mastocytosis with an associated haematological neoplasm	9741/3	CD117 (or other mast cell markers e.g. tryptase)	CD25, CD2, CD30, ki-67
Mast cell leukaemia	9742/3	CD117 (or other mast cell markers e.g. tryptase)	CD25, CD2, CD30, ki-67

Appendix B ISCL/EORTC staging system for mycosis fungoides and Sezary syndrome

The Union for International Cancer Control (UICC) does not provide TNM staging of primary cutaneous lymphomas, but the International Society for Cutaneous Lymphomas (ISCL) and the European Organisation of Research and Treatment of Cancer (EORTC) have proposed the following staging system for mycosis fungoides (MF) and Sezary syndrome (SS) (1946).

This classification system is used by some clinicians and multidisciplinary teams.

Table 1. ISCL/EORTC revision to the staging of MF and SS.

Reproduced from Olsen E *et al*.[31]

TNMB stages	
Skin	
T_1	Limited patches,* papules and/or plaques[+] covering <10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumours[++] (≥1cm diameter)
T_4	Confluence of erythema covering ≥80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes[§]; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative[#]
N_{1b}	Clone positive[#]
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative[#]
N_{2b}	Clone positive[#]
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation[$] and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells[&]
B_{0a}	Clone negative[#]
B_{0b}	Clone positive[#]
B_1	Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells[&] but does not meet the criteria for B_2
B_{1a}	Clone negative[#]

B_{1b}	Clone positive[#]
B_2	High blood tumour burden: ≥1000/ųl Sezary cells with positive clone[#]

* For skin, patch indicates any size skin lesion without significant elevation or induration. Presence or absence of hypo- or hyperpigmentation, scale, crusting and/or poikiloderma should be noted.

+ For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (>25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

++ For skin, tumour indicates at least one 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

[§] For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

[$] For viscera, spleen and liver may be diagnosed by imaging criteria.

[#] A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

[&] For blood, Sezary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sezary cells are not able to be used to determine tumour burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or more, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.

NCI, US National Cancer Institute; TCR, T-cell receptor; TNMB, tumour, node, metastasis, blood.

Table 2. Histopathological staging of lymph nodes in MF and SS.

Reproduced from Olsen E *et al*.[31]

Updated ISCL/ EORTC classification	**Dutch system[32]**	**NCI-VA classification[33–35]**
N_1	Grade 1: dermatopathic lymphadenopathy (DL)	LN_0: no atypical lymphocytes LN_1: occasional and isolated atypical lymphocytes (not arranged in clusters) LN_2: many atypical lymphocytes or in 3-6 cell clusters
N_2	Grade 2: DL; early involvement by MF (presence of cerebriform nuclei >7.5 ųm)	LN_3: aggregates of atypical lymphocytes; nodal architecture preserved
N_3	Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells (CMCs) Grade 4: complete effacement	LN_4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

LN, lymph node; NCI-VA, US National Cancer Institute-Veterans Administration.

The Union for International Cancer Control (UICC) does not provide a TNM staging of primary cutaneous lymphomas, but the International Society for Cutaneous Lymphomas (ISCL) and the European Organisation of Research and Treatment of Cancer (EORTC) have proposed the following staging system for primary cutaneous lymphomas other than MF and SS (1368A).

Table 3. ISCL/ EORTC proposed TNM staging of cutaneous lymphoma other than MF and SS.
Reproduced from Kim YH *et al.*[36]

Classification	
T	
T1	Solitary skin involvement
T1a	A solitary skin lesion <5 cm diameter
T1b	A solitary skin lesion >5 cm diameter
T2	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions*
T2a	All-disease encompassing in a <15 cm diameter circular area
T2b	All-disease encompassing in a >15 and <30 cm diameter circular area
T2c	All-disease encompassing in a >30 cm diameter circular area
T3	Generalised skin involvement
T3a	Multiple lesions involving 2 noncontiguous body regions
T3b	Multiple lesions involving ≥3 body regions
N	
N0	No clinical or pathologic lymph node involvement
N1	Involvement of 1 peripheral lymph node region[#] that drains an area of current or prior skin involvement
N2	Involvement of 2 or more peripheral lymph node regions[#] or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3	Involvement of central lymph nodes
M	
M0	No evidence of extracutaneous non-lymph node disease
M1	Extracutaneous non-lymph node disease present

* Definition of body regions (see Figure 1 of Kim YH *et al.*[33]): Head and neck: inferior border-superior border of clavicles, T1 spinous process. Chest: superior border-superior border of clavicles; inferior border-inferior margin of rib cage; lateral borders-mid-axillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border-inferior margin of rib cage; lateral borders-mid-axillary lines. Lower back/buttocks: superior border-inferior margin of rib cage; inferior border-inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders-mid-axillary lines. Each upper arm: superior borders-glenohumeral joints (exclusive of axillae); inferior borders-ulnar/radial-humeral (elbow) joint. Each lower fossae. Each lower leg/foot: superior borders-mid-patellae, mid popliteal fossae.

[#] Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, para-aortic, iliac.

Appendix C SNOMED coding

ICD-O-3	SNOMED RT code	Recommended SNOMED CT CONCEPT ID	SNOMED CT terminology
9700/3	M-97003	90120004	Mycosis fungoides (morphologic abnormality)
9701/3	M-97013	4950009	Sezary syndrome (morphologic abnormality)
9708/3	M-97083	103682005	Subcutaneous panniculitis-like T-cell lymphoma (morphologic abnormality)
9709/3	M-97093	28054005	Cutaneous T-cell lymphoma, no ICD-O subtype (morphologic abnormality)
9718/1	M-97181	397353001	Lymphomatoid papulosis (morphologic abnormality)
9718/3	M-97183	128804002	Primary cutaneous CD30 antigen positive T-cell lymphoproliferative disorder (morphologic abnormality)
9719/3	M-97193	128805001	Natural killer-/T-cell lymphoma, nasal and nasal-type (morphologic abnormality)
9725/3	M-97251	450907007	Hydroa vacciniforme-like lymphoma (morphologic abnormality)
9726/3	M-97263	450908002	Primary cutaneous gamma-delta T-cell lymphoma (morphologic abnormality)

Appendix D Guidance on the appropriateness of performing clonality tests

A study performed in the USA developed appropriate use criteria in dermatopathology by combining the best scientific evidence available with the collective judgement of experts to yield a statement of the appropriateness for performing a clonality assay in specific clinical scenarios encountered in everyday practice as outlined in Tables 3 and 4 below.[4,20,21] Tables 1 and 2 provide clear definitions of the histological features required for each category and a list of the clinical scenarios, for T and B-cell receptor clonality, respectively. The tables are slightly abbreviated versions of the ones in the original article. Please refer to the original article for further information. Please note that the international community (ISCL, EORTC and United States Cutaneous Lymphoma Consortium) use only 'diagnostic', 'consistent' and 'non-diagnostic' to define the clinic-pathologic diagnosis of mycosis fungoides (MF). Where it states 'concerning for', 'suspicious of' or 'suggestive of' MF in Table 1, this should be regarded as similar to 'consistent' for MF for the ISCL criteria with the caveat that 'consistent' means the clinical features are typical as per ISCL/EORTC criteria to confirm clinicopathologic diagnosis.[30]

Table 1. Lymphoproliferative definitions and clinical scenarios for T-cell receptor clonality.

Definitions
Diagnostic for MF • Presence of nearly all typical histopathologic diagnostic features of MF (atypical lymphocytes with hyperchromatic cerebriform nuclei surrounded by clear haloes, epidermotropism of solitary lymphocytes or clusters of atypical lymphocytes in the absence of spongiosis, epidermal lymphocytes larger than dermal lymphocytes). • Loss of 1 or more important T-cell marker (CD2, CD5 and/or CD7) within the neoplastic T-cell infiltrate along the dermoepidermal junction and/or in the epidermis. • Nearly all neoplastic cells express CD4 or CD8 (CD4 or CD8 significant predominance).
Consistent with MF • Histopathologic diagnostic criteria of MF are present. • Epidermotrophic atypical lymphocytes: – predominantly immunoreactive for CD2, CD3, CD4, CD5 and CD7 (partial) – predominantly immunoreactive for CD4 or CD8. • Loss of 1 or more mature T-cell markers (CD2, CD3, CD5 and CD7).
'Concerning for', 'suspicious of' or 'suggestive of' MF • Presence of 1 or more typical histopathologic diagnostic features of MF: – atypical lymphocytes with hyperchromatic, cerebriform nuclei surrounded by clear haloes – epidermotropism of solitary lymphocytes or clusters of atypical lymphocytes in the absence of spongiosis – epidermal lymphocytes larger than dermal lymphocytes – perivascular distribution of atypical lymphocytes ('bare underbelly sign') – papillary dermal fibrosis. • Normal immunophenotypical features: T-cell lymphoid infiltrate along the dermoepidermal junction and/or in the epidermis that is immunoreactive for CD2, CD3, CD5 and CD7 (partial or no loss) with a normal CD4:CD8 ratio.

'Not diagnostic for' MF • Limited/minimal/scant T-cell lymphoid infiltrate along the dermoepidermal junction and/or within the superficial dermal perivascular space. • Absence of lymphocyte epidermotropism or folliculotropism. • Absence of lymphocyte atypia. • Absence of papillary dermal fibrosis. • Normal immunophenotypical features: T-cell lymphoid infiltrate along the dermoepidermal junction and/or in the epidermis that is immunoreactive for CD2, CD3, CD5 and CD7 (partial or no loss) with a normal CD4:CD8 ratio.
Lymphomatoid papulosis (LyP) • Wedge-shaped mixed infiltrate if small and large lymphocytes with eosinophils and neutrophils, numerous CD30-positive large lymphocytes. • Or, scant to moderate mixed infiltrate with small and large lymphocytes with epidermotropism. • Or, dense diffuse infiltrate of large atypical CD30-positive lymphocytes.
Pityriasis lichenoides (PL) • Mixed lichenoid and spongiotic dermatitis with mounds of parakeratosis, extravasated erythrocytes; large cells present. • Or, wedge-shaped superficial and deep dermal lymphocytic infiltrate with extravasated erythrocytes (lymphocytic vasculitis), epidermal necrosis, parakeratosis, lichenoid reaction pattern; large cells present.
Clinical scenarios
1. Solitary or generalised scaly patches/plaques that are clinically concerning for MF (clinical impression: rule out MF or cutaneous T-cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' MF.
2. Clinical presentation of erythroderma with clinical impression of rule out MF, cutaneous T-cell lymphoma or Sezary syndrome (SS) and that is 'not diagnostic for' MF.
3. Clinical presentation of dermatitis with clinical impression of rule out MF or cutaneous T-cell lymphoma and that is 'not diagnostic for' MF.
4. Inflammatory/reactive papular or papulonecrotic eruption (solitary, regional or generalised) with clinical impression of LyP or PL, rule out MF or cutaneous T-cell lymphoma and histopathologic and immunophenotypic features typical for LyP or PL.
5. The development of T-cell cutaneous infiltrate that is 'not diagnostic for' MF but is present in a patient with a history of MF with a known T-cell clone (comparison of past and present clones).
6. The development of a T-cell cutaneous infiltrate in a patient with a history of systemic T-cell lymphoma.
7. A cutaneous T-cell infiltrate with a folliculotropic rather than epidermotropic T-cell infiltrate.
8. Pigmented purpuric patches (solitary, regional or generalised) and clinical impression of rule out MF or cutaneous T-cell lymphoma and histopathologic and immunophenotypic features that are 'not diagnostic for' MF.
9. Clinically reactive entities (see reference for individual diagnoses) with histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' MF.

10. Pre-existing diagnosis of MF and new or evolving lesions similar to original lesions with clinical impression of rule out MF and histopathologic and immunophenotypic features 'consistent with' MF.
11. Development of nodules in a patient with MF that are histologically 'concerning for', 'suspicious of' or 'suggestive of' large cell transformation with CD30 positivity.
12. Development of nodules in a patient with MF that are histologically 'concerning for', 'suspicious of' or 'suggestive of' large cell transformation without CD30 positivity.

Table 2. Lymphoproliferative definitions and clinical scenarios for B-cell receptor (IgH) clonality.

Definitions
'Consistent with' cutaneous marginal zone lymphoma or follicle centre lymphoma (FCL) • Histopathologic diagnostic criteria of cutaneous marginal zone lymphoma or FCL are present. • Predominance of B-cells. • B-cells cannot be explained by normal architecture (i.e. confined to lymphoid follicles). Light chain restriction is present by protein immunohistochemistry (kappa and lambda) or mRNA chromogenic ISH (kappa and lambda).
'Concerning for', 'suspicious of' or 'suggestive of' cutaneous marginal zone lymphoma • Presence of 1 or more typical histopathological features of cutaneous marginal zone lymphoma (Grenz zone, predominance of plasma cells, 'bottom heavy' infiltrate, superficial and deep perivascular and periadnexal infiltrate, nodular infiltrate with periphery of plasma cells and numerous 'monocytoid' B-cells, diffuse infiltrate of monotonous lymphocytes). • Normal immunophenotypical features (mixed B- and T-cell infiltrate).
'Concerning for', 'suspicious of' or 'suggestive of' FCL • Presence of 1 or more typical histopathologic features of FCL (Grenz zone, predominance of cleaved cells (centrocytes) and/ or large noncleaved cells (centroblasts), nodular infiltrate composed of disorganised follicles, 'bottom heavy' infiltrate, follicle-like structures without tangible body macrophages, diffuse infiltrate of monotonous small cleaved or large noncleaved lymphocytes). • Normal immunophenotypical features (mixed B- and T-cell infiltrate, B-cells confined to follicles, high ki-67 proliferative rate within follicles, lack of BCL-6+, CD10+ B-cells outside of follicles).
'Not diagnostic for' cutaneous B-cell lymphoma (cutaneous marginal zone lymphoma or FCL) • Grenz zone is absent and there is epidermal involvement by lymphocytes. • Scant (less than 200 lymphoid cells) infiltrate. • Minimal number of B-cells within a nodular or diffuse infiltrate. • No light chain restriction as measured by protein immunohistochemistry (kappa and lambda); no light chain restriction as measured by mRNA chromogenic ISH (kappa and lambda).

‘Concerning for’, ‘suspicious of’ or ‘suggestive of’ cutaneous diffuse large B-cell lymphoma, leg type
• Presence of 1 or more typical histopathologic features of diffuse large B-cell lymphoma, leg type: – Grenz zone, predominance of large immunoblastic cells – diffuse infiltrate, necrosis and easily observable mitotic activity in neoplastic appearing cells. • Predominance of B-cells on immunohistochemistry.
Clinical scenarios
1. Solitary or multiple erythematous nodules that are clinically concerning for cutaneous B-cell lymphoma (clinical impression- rule out B-cell lymphoma) and that are histologically and immunophenotypically ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ cutaneous marginal zone lymphoma.
2. Solitary or multiple erythematous nodules that are clinically concerning for cutaneous B-cell lymphoma (clinical impression – rule out B-cell lymphoma) and that are histologically and immunophenotypically ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ FCL.
3. Clinical presentation of solitary or multiple nodules with clinical impression of cutaneous lymphoid hyperplasia and that are histologically and immunophenotypically ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ cutaneous marginal zone lymphoma.
4. Clinical presentation of solitary or multiple nodules with clinical impression of cutaneous lymphoid hyperplasia and that are histologically and immunophenotypically ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ FCL.
5. Clinical presentation of solitary or multiple nodules with clinical impression of rule out cutaneous B-cell lymphoma (cutaneous marginal zone or FCL) and that is ‘not diagnostic for’ cutaneous B-cell lymphoma.
6. Clinical presentation of a solitary lesion, suggestive of a non-neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a predominance of B-cells immunophenotypically.
7. Clinical presentation of a dermatitis, suggestive of a non-neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a predominance of B-cells immunophenotypically.
8. Unknown history, but histopathologic and immunophenotypic features ‘consistent with’ cutaneous marginal zone lymphoma or FCL.
9. Pre-existing diagnosis of cutaneous B-cell lymphoma (cutaneous marginal zone or FCL) and new or evolving lesions similar to original lesions with clinical impression of rule out cutaneous B-cell lymphoma and histopathologic and immunophenotypic features ‘consistent with’ cutaneous marginal zone lymphoma or FCL.
10. Solitary or multiple erythematous nodules that are clinically concerning for an aggressive B-cell lymphoma (clinical impression – rule out B-cell lymphoma, leg type) and that are histologically and immunophenotypically ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ cutaneous diffuse large B-cell lymphoma, leg type.
11. The development of a B-cell cutaneous infiltrate that is not diagnostic for cutaneous B-cell lymphoma in a patient with a history of cutaneous B-cell lymphoma with a known B-cell clone (comparison of past and present clones).
12. The development of a B-cell cutaneous infiltrate in a patient with a history of any systemic B-cell lymphoma.

13. Other more aggressive cutaneous B-cell lymphomas other than cutaneous diffuse large B-cell lymphoma, leg type, such as intravascular large B-cell lymphoma or cutaneous plasmablastic lymphoma.

Table 3. Lymphoproliferative T-cell clonality appropriate use scores (refer to Table 1 for complete wording of clinical scenarios and associated definitions).

Clinical scenario	Appropriate use score
≥1 scaly patches/plaques concerning for MF and IHC 'concerning', 'suspicious' or 'suggestive or' MF	Usually appropriate
Erythroderma; clinical r/o MF/CTCL/SS; histology 'not diagnostic' for MF	No consensus
Dermatitis; clinical r/o MF/CTCL; histology 'not diagnostic' for MF	Rarely appropriate
Inflammatory/reactive/papular/papulonecrotic solitary/regional/generalised; clinical r/o LyP, PL, MF, CTCL; histology typical for LyP or PL	Rarely appropriate
Histology of a T cell infiltrate 'not diagnostic for MF' in patient with history of MF and known clone (comparison of past and present clone)	Usually appropriate
T cell infiltrate in patient with history of systemic T-cell lymphoma	Majority usually appropriate
Histology of a folliculotropic T-cell infiltrate	Usually appropriate
Pigmented purpuric rashes solitary/ regional/ generalised; clinical r/o MF/CTCL; histology 'not diagnostic' for MF	Rarely appropriate
Clinical reactive entities; histology and IHC 'concerning', 'suspicious; or 'suggestive of' MF	Uncertain appropriateness
New/evolving lesion in patient with history of MF; clinical r/o MF; histology and IHC 'consistent with' MF	No consensus
Nodules in patient with history of MF; histology 'concerning', 'suspicious' or 'suggestive of' MF with CD30+ large cell transformation	Rarely appropriate
Nodules in patient with history of MF; histology 'concerning', 'suspicious' or 'suggestive of' MF without CD30+ large cell transformation	Rarely appropriate

CTCL, cutaneous T-cell lymphoma; IHC, immunophenotype; LyP, lymphomatoid papulosis; MF, mycosis fungoides; PL, pityriasis lichenoides; r/o, rule out.

Table 4. Lymphoproliferative B-cell receptor (IgH) gene rearrangement by PCR appropriate use scores (refer to Table 2 for complete wording of clinical scenarios and associated definitions)

Clinical scenario	Appropriate use score
≥1 erythematous concerning nodules; clinical r/o B-cell lymphoma; histology and IHC 'concerning for', 'suspicious of' or 'suggestive of' PCMZL	Usually appropriate
≥1 erythematous concerning nodules; clinical r/o B-cell lymphoma; histology and IHC 'concerning for', 'suspicious of' or 'suggestive of' FCL	Usually appropriate
≥1 nodules; clinical CLH; histology and IHC 'concerning for', 'suspicious of' or 'suggestive of' PCMZL	Usually appropriate

≥1 nodules; clinical CLH; histology and IHC ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ FCL	Usually appropriate
≥1 erythematous concerning nodules; clinical r/o B-cell lymphoma (PCMZL OR FCL); histology and IHC ‘not diagnostic’ for cutaneous B-cell lymphoma	Rarely appropriate
1 lesion; clinical s/o non-neoplastic process; B-cell predominant infiltrate	Majority usually appropriate
Dermatitis; clinical s/o non-neoplastic process; B-cell predominant infiltrate	Majority usually appropriate
Unknown history; histology and IHC ‘consistent with’ PCMZL or FCL	No consensus
New/evolving lesion in patient with prior ddx of B-cell lymphoma (PCMZL or FCL); clinical r/o B-cell lymphoma; histology and IHC ‘consistent with’ PCMZL or FCL	Rarely appropriate
≥1 nodules; clinical concerning for aggressive B-cell lymphoma r/o B-cell lymphoma, leg type; histology and IHC ‘concerning for’, ‘suspicious of’ or ‘suggestive of’ PCLBCL, LT	Usually appropriate
Cutaneous B-cell infiltrate not diagnostic for B-cell lymphoma but in a patient with history of B-cell lymphoma known clone (comparison of past and present clones)	Usually appropriate
Cutaneous B-cell infiltrate in a patient with history of any systemic B-cell lymphoma	Majority usually appropriate
Other more aggressive cutaneous B-cell lymphoma other than PCLBCL, LT (e.g. IVL or cutaneous plasmablastic lymphoma)	No consensus

CLH, Cutaneous lymphoid hyperplasia; FCL, follicle centre lymphoma; IHC, immunophenotype; IVL, intravascular lymphoma; PCLBCL, LT, primary cutaneous large B-cell lymphoma, leg type; PCMZL, primary cutaneous marginal zone lymphoma; r/o, rule out.

Appendix E Reporting proforma for primary cutaneous lymphoma specimens

Surname: …… Forenames: ..…… Date of Birth: …… Sex: ...…..

Referring organisation: ...…… Hospital No: …… NHS No:……

Biopsy taker: …… Caring physician: ……

Specimen number (referring organisation): ...…… Reporting organisation: ……

Specimen number (reporting organisation): …… Date of biopsy: ……..…….

Date of dispatch from referring organisation: …….. Date of receipt: ……

Date of final report: ……..……. Pathologist:……

Clinical context and relevant clinical history:

Clinical photographs: ☐ Yes ☐ No

Immunosupression: ☐ Yes ☐ No

If yes state reason: ……

Previous diagnosis of lymphoma: ☐ Cutaneous ☐ Systemic ☐

If yes specify type: ……

Are previous biopsies available: ☐ Yes ☐ No

If yes, are they available for evaluation: ☐ Yes ☐ No

Site of lesion: ……..

Focality: Unifocal ☐ Multifocal ☐ Indeterminate ☐

Indication for investigation

Primary diagnosis ☐ Staging ☐ Re-staging ☐ Clinical trial ☐

Specimen type

Excision biopsy ☐ Incisional biopsy ☐ Punch biopsy ☐

Other biopsy (specify) ……....

Fresh tissue sampling

Yes ☐ No ☐

Flow cytometry/ genetic/ molecular testing (specify) ……....

Specimen description

Number of specimens:

Sites: ……. Size (s) ……..x……..x…....mm, ……..x……..x…....mm

Macroscopic description …….

Provisional (referring) diagnosis

Tumour type

WHO entity diagnosis:

ICD-O morphology code:

(If diagnosis is incomplete/ uncertain, provide reasons):

Clinical context:

Corroborated by clinical context ☐ Not corroborated by clinical context ☐ Not applicable ☐

Microscopic description (morphology)

……..

Margin status (where applicable)

Additional studies:

Immunophenotype:

In-situ hybridisation for EBER: …….

Genotype and clonality (FISH, PCR for clonality, mutational analysis): ……

Other investigations (specify): ……..

Final report interpretation and summary

ISCL/ EORTC Stage

T……..... N……..... M……..... B……....

SNOMED codes T..... M.....

Pathologist …….. **Date**……/……/……

Appendix F Reporting proforma for primary cutaneous lymphoma specimens in list format

Element name	Values	Implementation comments	COSD v9
Surname; Forenames; Date of birth; Sex; Referring organisation; Hospital No; NHS No; Biopsy taker; Caring physician; Specimen number (referring organisation); Reporting organisation; Specimen number (reporting organisation); Date of biopsy; Date of dispatch from referring organisation; Date of receipt; Date of final report; Pathologist; Clinical context and relevant clinical history	Free text		
Clinical photographs including clinical photograph, immunosuppression status and presence or absence of known systemic lymphoma	Single selection value list: • Yes • No (Attach photographs or link to access photographs via a secure website)		
Immunosuppression	Single selection value list: • Yes • No	If yes, state reason (free text)	
Previous diagnosis of lymphoma	Multiple selection value list: • Cutaneous • Systemic	If yes, specify type (free text)	
Are previous biopsies available	Single selection value list: • Yes • No	If yes, are they available for evaluation: Single selection value list: • Yes • No	
Site of lesion	Free text		

Focality	Single selection value list: • Unifocal • Multifocal • Indeterminate		
Indication for investigation	Multiple selection value list: • Primary diagnosis • Staging • Re-staging • Clinical trial		
Specimen type	Single selection value list: • Excision biopsy • Incisional biopsy • Punch biopsy • Other biopsy (specify)	If 'Other biopsy', specify	pCR0760 Excision biopsy = (EX) Excision Incisional biopsy = (IB) Incisional Biopsy Punch biopsy = (PB) Punch biopsy Other biopsy = (BU) Biopsy NOS
Fresh tissue sampling	Single/Multiple selection value list: • Yes • No • Flow cytometry/ genetic/ molecular testing (specify)	If 'Flow cytometry/genetic/molecular testing,' specify	
Specimen description			
Number of specimens			
Sites	Free text		
Size	Size in mm x 3		
Macroscopic description	Free text		
Provisional (referring) diagnosis			
Tumour type			
WHO entity diagnosis	Free text		
ICD-O morphology code	Free text (Look up from ICD-O tables)		
If diagnosis is incomplete/ uncertain, provide reasons	Free text		

Clinical context	Single selection value list: • Corroborated by clinical context • Not corroborated by clinical context • Not applicable		
Microscopic description (morphology)			
Immunophenotype:	Free text		
In-situ hybridisation for EBER:	Free text		
Genotype and clonality (FISH, PCR for clonality, mutational analysis):	Free text		
Other investigations (specify)	Free text		
Final report interpretation and summary	Free text		
ISCL/ EORTC Stage			
T Stage	Free text		pCR0910
N Stage	Free text		pCR0920
M Stage	Free text		pCR0930
B Stage	Free text		
SNOMED T Code	May have multiple codes. Look up from SNOMED tables.		pCR6410
SNOMED M Code	May have multiple codes. Look up from SNOMED tables.		pCR6420

Appendix G Summary table – explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type. or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type. or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type. or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion. or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix H AGREE II guideline monitoring sheet

The Cancer Datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this Dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–9
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–9
16 The different options for management of the condition or health issue are clearly presented	2–9
17 Key recommendations are easily identifiable	2–9
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–G
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	10
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword