TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUE STRUCTURED REPORTING PROTOCOL

(1st Edition 2010)

ISBN: 978-1-74187-455-6 (online)

Publications number (SHPN): (CI) 090266

Online copyright

First published: Feb 2010, 1st Edition (Version 1.0)

Disclaimer

The Royal College of Pathologists of Australasia ("College") has developed these protocols as an educational tool to assist pathologists in reporting of relevant information for specific cancers. While each protocol includes “standards” and “guidelines” which are indicators of ‘minimum requirements’ and ‘recommendations’, the protocols are a first edition and have not been through a full cycle of use, review and refinement. Therefore, in this edition, the inclusion of “standards” and “guidelines” in each document are provided as an indication of the opinion of the relevant expert authoring group, but should not be regarded as definitive or as widely accepted peer professional opinion. The use of these standards and guidelines is subject to the clinician’s judgement in each individual case.

The College makes all reasonable efforts to ensure the quality and accuracy of the protocols and to update the protocols regularly. However subject to any warranties, terms or conditions which may be implied by law and which cannot be excluded, the protocols are provided on an "as is" basis. The College does not warrant or represent that the protocols are complete, accurate, error-free, or up to date. The protocols do not constitute medical or professional advice. Users should obtain appropriate medical or professional advice, or where appropriately qualified, exercise their own professional judgement relevant to their own particular circumstances. Users are responsible for evaluating the suitability, accuracy, currency, completeness and fitness for purpose of the protocols.

Except as set out in this paragraph, the College excludes: (i) all warranties, terms and conditions relating in any way to; and (ii) all liability (including for negligence) in respect of any loss or damage (including direct, special, indirect or consequential loss or damage, loss of revenue, loss of expectation, unavailability of systems, loss of data, personal injury or property damage) arising in any way from or in connection with; the protocols or any use thereof. Where any statute implies any term, condition or warranty in connection with the provision or use of the protocols, and that statute prohibits the exclusion of that term, condition or warranty, then such term, condition or warranty is not excluded. To the extent permitted by law, the College's liability under or for breach of any such term, condition or warranty is limited to the resupply or replacement of services or goods.

Contents

Scope

This protocol contains standards and guidelines for the preparation of structured reports for tumours of haematopoietic and lymphoid tissue. The standards, guidelines and commentary presented here relate primarily to the diagnosis of B, T and natural killer (NK) lymphoid neoplasms as defined by the WHO classification, including those with a leukaemic presentation. However, the protocol can equally well be used for reporting neoplasms of myeloid cells, histiocytic and dendritic cells, and cases of indeterminate lineage. It can also be adapted for use with any specimen type, including bone marrow aspirate and trephine, peripheral blood and cytology specimens.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians, and improve decision support for cancer treatment. The protocol provides the framework for the reporting of any tumours of haematopoietic and lymphoid tissue, whether as a minimum data set or fully comprehensive report

Abbreviations

AJCC	American Joint Committee on Cancer
ATLL	adult T-cell leukaemia /lymphoma
EBV	Epstein-Barr virus
FLIPI	Follicular Lymphoma International Prognostic Index
FNA	fine needle aspirate
HHV	human herpesvirus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HTLV	human T-lymphotrophic virus
ICD-O-3	International Classification of Diseases for Oncology
IPI	International Prognostic Index
LDH	lactic dehydrogenase
LIS	laboratory information systems
MIPI	Mantle cell lymphoma International Prognostic Index
NHL	non-Hodgkin lymphoma
NK	natural killer [cell]
PBS	Pharmaceutical Benefits Scheme
RCPA	Royal College of Pathologists of Australasia
TNFα	tumour necrosis factor
TNM	tumour-node-metastasis
WBC	white blood cell count
WHO	World Health Organization

Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for ‘standard’, ‘guideline’ and ‘commentary’, because these form the basis of the protocol.

Ancillary study	An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.
Clinical information	Patient information required to inform pathological assessment, usually provided with the specimen request form. Also referred to as ‘pretest information’.
Commentary	Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary). Commentary is used to: • define the way an item should be reported, to foster reproducibility • explain why an item is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer). • cite published evidence in support of the standard or guideline • clearly state any exceptions to a standard or guideline. In this document, commentary is prefixed with ‘CS’ (for commentary on a standard) or ‘CG’ (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (eg CS1.01a, CG2.05b).
General commentary	General commentary is text that is not associated with a specific standard or guideline. It is used: • to provide a brief introduction to a chapter, if necessary • for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).

Guideline	Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are not essential for clinical management, staging or prognosis of a cancer, but are recommended. Guidelines include key observational and interpretative findings that are fundamental to the diagnosis and conclusion. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail. Guidelines are not used for research items. In this document, guidelines are prefixed with 'G' and numbered consecutively within each chapter (eg G1.10).
Macroscopic findings	Measurements, or assessment of a biopsy specimen made by the unaided eye.
Microscopic findings	In this document, the term 'microscopic findings' refers to histological or morphological assessment.
Standard	Standards are mandatory, as indicated by the use of the term 'must'. Their use is reserved for core items essential for the clinical management, staging or prognosis of the cancer. The summation of all standards represents the minimum dataset for the cancer. In this document, standards are prefixed with 'S' and numbered consecutively within each chapter (eg **S1.02**).
Structured report	A report format which utilizes standard headings, definitions and nomenclature with required information.
Synoptic report	A structured report in condensed form (as a synopsis or precis).
Synthesis	Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new. In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more chapters to derive new information

Introduction

Lymphoma

Lymphoma is the sixth most common cancer in Australians, with more than 4000 new cases diagnosed in 2003,[1] representing 4.4% of all newly diagnosed cancers and accounting for 4.1% of all cancer deaths. If classified according to World Health Organization (WHO) classification terminology,[2] including chronic lymphocytic leukaemia and plasma cell myeloma in the total, 6482 malignant lymphoid neoplasms were diagnosed in 2003.[1] The age-standardised rate for lymphoma in 2003 was 20.3/10^5 persons (male and female). The incidence of lymphoma has been increasing steadily over the decades. The incidence of lymphoma in Australia rose by >35% between 1993 and 2003,[1] and a similar increase is projected for the decade 2002–2011.[3] Similar statistics are to be found in the Surveillance, Epidemiology and End Results (SEER) data.[4]

Perhaps no other field of cancer presents the diagnostic and management complexities of lymphomas. In the most recent revision of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues,[2]aside from the immunodeficiency-associated lymphoproliferative disorders and histiocytic and dendritic cell neoplasms, there are more than 70 non-Hodgkin lymphoma (NHL) entities (diseases) and 6 subtypes of Hodgkin lymphoma.[1] Each disease in the classification is defined by a combination of its morphological, immunophenotypic, genetic and clinical features. National Health and Medical Research Council (NHMRC)-approved clinical practice guidelines for the diagnosis and management of lymphoma in Australia were published in 2005, following an initiative of the Cancer Council Australia and Australian Cancer Network.[5] Adherence to the principles described in these two publications[2,5] should ensure best practice both in the pathology laboratory and clinically, for patients with lymphoma.

Benefits of structured reporting

The traditional narrative style used in the histopathological reporting of cancer, in the face of ever-increasing numbers of pathological parameters required for inclusion in a clinically relevant histopathology report, may lead to the omission of critical information necessary for patient management. This has long been recognised[6-8] and has led to the promulgation of minimum datasets[9-10] or comprehensive checklists for the reporting of cancer at virtually all anatomical sites.[11-12] While minimum datasets and checklists are accepted as essential tools for adequate reporting, the presentation of the large amount of information in a user-friendly and useful manner is key. The structured report is a logical extension of minimum datasets and reporting checklists in anatomical pathology. Given the large volume of information from multiple sources that needs to be considered in formulating a lymphoma diagnosis, structured reporting of lymphomas is overdue. It has already been shown in other organ systems that structured reporting improves the quality and uniformity of information provided in the pathology report.[13-16] Further, accreditation of cancer centres in the United States since January 2004 is linked to the provision of data in pathology reports deemed essential by the College of American Pathologists.[17-18] While there has been little published relating to lymphoma structured reporting, this approach is readily applicable in the field of haematopathology.[19-20]

Areas of uncertainty

The role of the pathologist is critical in establishing the correct lymphoma diagnosis. Based on the pathological findings, appropriate treatment and management based on prognosis of the condition are enabled and research facilitated. Lymphoma diagnosis is often difficult, not only because of the bewildering spectrum of histological appearances and immunophenotypes, but also because of inconsistent availability of essential ancillary testing outside tertiary or academic settings. Further, experience in lymphoma diagnosis varies among pathologists and auditing of histopathology reporting has confirmed that

areas of diagnostic difficulty are to be found, particularly in lymphoma diagnosis and classification. The protocol is designed with this in mind.

Design of this protocol

This protocol defines the relevant information to be assessed and recorded in a pathology report for lymphoma, but it is sufficiently flexible to allow for recording of diagnostic uncertainty or nuance. Mandatory elements (standards) are differentiated from those that are not mandatory but are recommended (guidelines). Also, items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. The structure provided by the following chapters, headings and subheadings describes the elements of information and their groupings, but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

When two or more disparate lymphomas are identified in one biopsy episode they are designated “composite lymphoma” and usually incorporated in one report. If preferred, such cases may be described in separate protocols.

Key documentation

- *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols, Royal College of Pathologists of Australasia*[21]
- *Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma, Australian Cancer Network, 2007*[5]
- *AJCC Cancer Staging Manual*, 7th edition, American Joint Committee on Cancer 2010[22]
- *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers,* Royal College of Pathologists of Australasia, 2004[23]
- *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*, 4th edition, World Health Organization Classification of Tumours 2008[2]
- Report of the Association of Directors of Anatomic and Surgical Pathology.[11]

Changes since the last edition

Not applicable

Authority and development

This section provides details of the committee involved in developing this protocol and the process by which it was developed.

Protocol developers

This protocol was developed by an expert committee, with assistance from relevant stakeholders.

Expert committee

Dr Debbie Norris, (Chair and lead author) Anatomical Pathologist

Associate Professor David Ellis, Anatomical Pathologist

Dr Malcolm Green, Haematologist

Dr David Joske, Haematologist

Associate Professor Peter Macardle Ph.D. Chief Medical Scientist

Associate Professor John Miliauskas, Anatomical Pathologist

Clin. Professor Dominic Spagnolo, Anatomical Pathologist

Dr Jennifer Turner, Anatomical Pathologist

International Liaison

Dr Jerry Hussong, Anatomical Pathologist, College of American Pathologists

Acknowledgements

The Lymphoma expert committee wish to thank all the pathologists and clinicians who contributed to the discussion around this document.

Stakeholders

ACT Health
Anatomical Pathology Advisory Committee (APAC)
Australian Association of Pathology Practices Inc (AAPP)
Australian Blood Cancer Registry (ABCR)
Australian Cancer Network
Australian Commission on Safety and Quality in Health Care
Cancer Australia
Cancer Council ACT
Cancer Council NSW
Cancer Council Queensland
Cancer Council SA
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer specific expert groups – engaged in the development of the protocols
Cancer Voices

Clinical Oncology Society of Australia (COSA)
Colorectal Cancer Research Consortium
Department of Health and Ageing
Grampians Integrated Cancer Services (GICS)
Health Informatics Society of Australia (HISA)
Medical Software Industry Association (MSIA)
National Breast and Ovarian Cancer Centre (NBOCC)
National Coalition of Public Pathology (NCOPP)
National E-Health Transition Authority (NEHTA)
National Pathology Accreditation Advisory Council (NPAAC)
National Round Table Working Party for Structured Pathology Reporting of Cancer.
New Zealand Guidelines Group (NZGG)
NSW Department of Health
Peter MacCallum Cancer Institute
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
Southern Cancer Network, Christchurch, New Zealand
Southern Melbourne Integrated Cancer Service (SMICS)
Standards Australia
The Australasian Leukaemia and Lymphoma Group (ALLG)
The Haematology Society of Australia & New Zealand (HSANZ)
The Medical Oncology Group of Australia
The Royal Australasian College of Surgeons (RACS)
The Royal Australian and New Zealand College of Radiologists (RANZCR)
The Royal Australian College of General Practitioners (RACGP)
The Royal College of Pathologists of Australasia (RCPA)
Victoria Cancer Council
Victorian Cooperative Oncology Group (VCOG)
Western Australia Clinical Oncology Group (WACOG)

Secretariat

Anna Burnham, Cancer Institute NSW

Meagan Judge, Royal College of Pathologists of Australasia

Medical editor

Janet Salisbury, Biotext

Development process

This protocol has been developed following the seven-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*[21]

Where no reference is provided, the authority is the consensus of the expert group.

1 Clinical information and surgical handling

This chapter relates to information that should be collected before the pathology test, and procedures that are required before handover of specimens to the laboratory. Some of this information can be collected on generic pathology request forms; any additional information required specifically for the reporting of lymphoma may be recorded on a separate data sheet. Appendix 1 provides a standardised data sheet that may be useful in obtaining all relevant information**.**

Knowledge of the clinical presentation is an essential part of the WHO classification yet it may not be available to the reporting pathologist for a number of reasons:

- The clinical assessment and staging may be incomplete at the time of biopsy.
- The pathology request is often authored by the clinician performing the biopsy rather than the clinician who is investigating and managing the patient.
- The identity of this clinician is often not indicated on the pathology request form

In practice therefore, much of the information in the following guidelines may not be available to the pathologist upon receipt of the specimen. It is important in such cases that the reporting pathologist should be able to communicate with the managing clinician for clarification (see S1.02).

For each guideline, it is good practice to record 'Unknown' where appropriate since this will alert the reader if the pathologist is unaware of important clinical information which may impact upon the diagnosis.

Patient and clinician information

S1.01 The Royal College of Pathologists of Australasia (RCPA) *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers* must be adhered to.[23]

CS1.01a This document specifies the minimum information to be provided by the requesting clinician for any pathology test. Items relevant to cancer reporting protocols include:

- patient name
- date of birth and sex
- identification and contact details of requesting doctor
- type of specimen
- date of request
- clinical information relevant to the investigations requested should be quoted verbatim.

G1.01 The patient's health identifiers should be recorded where provided.

CG1.01a The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a NHI or UHI.

G1.02 The pathology accession number of the specimen should be recorded

S1.02 The principal clinician involved in the patient's care and responsible for investigating the patient must be identified.

CS1.02a The requesting clinician (identified under S1.01) is often the doctor who performs the surgery or biopsy, and may not be the person with overall responsibility for investigating and managing the patient. Identification of the principal clinician is essential, to ensure that clinical information is communicated effectively. It is also useful if further information about the patient is needed in order to make correct diagnosis.

CS1.02b Typically, this will be a haematologist, medical oncologist or radiation oncologist, but it may be a general practitioner or general physician.

Current biopsy information

S1.03 The site of biopsy must be recorded.

CS1.03a The site of the biopsy is recorded as:

- lymph node (specify)
- other (specify).

CS1.03b Site information is important for accurate diagnostic subtyping because certain types of lymphoma have a predilection for certain sites.

CS1.03c When more than one biopsy has been performed, site information helps define which biopsy the report refers to.

S1.04 The laterality must be recorded.

CS1.04a Laterality is recorded as:

- left
- midline
- right
- unknown

CS1.04b When more than one biopsy has been performed, laterality information helps define which biopsy the report refers to.

G1.03 The reason for the biopsy should be recorded.

CG1.03a Possible descriptors include:

- primary diagnosis
- staging
- relapse
- for assessment of transformation.

CG1.03b Diagnostic criteria may be less stringent for staging or relapse than for primary diagnosis.

CG1.03c This information can alert the pathologist to previous biopsies.

Current disease status

G1.04 The clinical diagnosis or differential diagnosis should be recorded.

G1.05 Involved sites or pattern of disease spread and whether disease is nodal or extranodal should be recorded if known

CG1.05a Certain types of lymphoma have a predilection for specific primary sites and/or pattern of disease spread. This information is therefore important for accurate WHO subtyping.

CG1.05b Certain diseases have a predilection for nodal or extranodal sites of involvement. For example, extranodal marginal zone lymphomas arise in extranodal extralymphatic sites such as gastrointestinal tract, salivary gland and thyroid. Primary Hodgkin lymphoma is rare in extranodal sites.

For some lymphomas, whether the disease is nodal or extranodal has prognostic significance. For example primary cutaneous follicle centre lymphoma has a survival >95% and tendency to local recurrence, and grading is irrelevant to treatment or prognosis, whereas in nodal follicular lymphoma, grading is required and prognosis is closely related to extent of disease at diagnosis—Follicular Lymphoma International Prognostic Index (FLIPI) being a strong predictor of outcome.[24]

The AJCC staging system[22,26], modified from the Ann Arbor staging protocol, differentiates between lymphatic sites (lymph nodes, Waldeyer's ring, thymus or spleen), and extralymphatic sites.

CG1.05c Recommended descriptors are:

- nodal or lymphatic
- extranodal or extralymphatic
- nodal and extranodal
- unknown.

G1.06 An estimation of stage or extent of disease should be given if possible

CG1.06a Tumour bulk is an important prognostic factor, and is an element of staging.[22,24-26]

Ann Arbor stage is rarely known at the time of biopsy but an estimate of the extent of disease may influence the diagnosis. For example, nodular lymphocyte predominant Hodgkin lymphoma usually presents with solitary or localised lymphadenopathy, whereas angioimmunoblastic T-cell lymphoma typically presents with generalised disease.

CG1.06b An estimate of disease extent may be adequately recorded for pathological assessment as:

- solitary
- localised
- generalised
- unknown.

G1.07 All relevant constitutional symptoms should be recorded

CG1.07a A history of constitutional symptoms may provide clues to the diagnosis since they constitute part of the typical clinicopathological picture of some lymphomas, but not others.

CG1.07b Constitutional symptoms are known to be of prognostic value in NHL (across all stages) in the Ann Arbor and AJCC/TNM staging).[22,26] Systemic symptoms of fever greater than 38.3°C, unexplained weight loss and night sweats are used to define two categories for each stage of NHL:

- A (symptoms absent)
- B (symptoms present).[2,4,11,17,27-28]

Poor patient 'performance status', relating to the overall activity level of the patient, also has prognostic significance.[1,3]

Appendix 5 includes further information on AJCC/TNM staging.

CG1.07c Constitutional symptoms may be listed individually but for pathological assessment it may be sufficient to record constitutional symptoms as:

- present
- absent
- unknown.

G1.08 All relevant laboratory test results should be recorded

CG1.08a These findings may form an important and integral part of the clinicopathological picture that allows the specific diagnosis to be made (eg IgM paraprotein in Waldenstrom macroglobulinaemia, peripheral blood lymphocyte count in distinguishing lymphomas from lymphoid leukaemias). Some abnormal laboratory tests are characteristic of certain WHO subtypes. An example is polyclonal hypergammaglobulinaemia in angioimmunoblastic T-cell lymphoma. Others are important in prognosis. For example, anaemia and elevated serum lactate dehydrogenase (LDH) level are adverse prognostic factors and are element of the International Prognostic Index and the Follicular Lymphoma International Prognostic Index.[4-5,8,12,16,20-23,29 24,30]

Appendix 6 includes further information on prognostic indexes.

Relevant history

G1.09 Any previous lymphoma, leukaemia or other relevant haematological disease should be recorded.

CG1.09a This may be important for a number of reasons:

- Confirmation of the original diagnosis (for recurrent disease).
- Identification of further ancillary studies. For example, flow cytometry studies not available on one biopsy may have been performed on a preceding fine needle aspirate (FNA) biopsy
- To provide evidence of transformation or tumour progression

- Identification of a new, possibly unrelated lymphoma.

CG1.09b The WHO category should be given where possible. If the history is not given, record it as 'unknown'. This provides feedback to the clinicians that the pathologist is unaware of any previous relevant disease.

CG1.09c Details of relevant previous biopsies should be recorded where possible:

- date of biopsy
- site of biopsy
- type of biopsy
- laboratory
- laboratory reference numbers.

G1.10 Any previous relevant treatment should be recorded.

CG1.10a Recent therapy may alter the morphological appearances, potentially affecting interpretation.

Immunotherapy is particularly important as it may change the tumour immunophenotype

G1.11 Predisposing factors such as immunocompromised states (immunodeficiency associated lymphoproliferative disorders) and autoimmune conditions should be recorded.

CG1.11a Immunodeficiency–associated lymphoproliferative disorders as defined by the WHO 2008[2] are:

- lymphoproliferative diseases associated with primary immune disorders (congenital immunodeficiency)
- lymphomas associated with HIV infection
- post-transplant lymphoproliferative disorders
- other iatrogenic immunodeficiency-associated lymphoproliferative disorders including immunosuppressive drugs such as methotrexate, and antagonists of TNFα(such as infliximab).

CG1.11b Immunocompromise is associated with increased rates of lymphoproliferative disease including B-cell and T-cell lymphomas, Hodgkin lymphoma, and lymphoid proliferations of uncertain malignant potential. Certain WHO entities are defined by the nature of immunodeficiency eg methotrexate-related lymphoproliferative disease.

CG1.11c Certain autoimmune disorders are associated with increased rates of NHL overall, and with certain B-cell and T-cell NHL subtypes.[31]

CG1.11d Autoimmune disorders include:

- Sjögren syndrome
- Hashimoto thyroiditis
- rheumatoid disease
- systemic lupus erythematosus
- coeliac disease

- psoriasis.

G1.12 Predisposing factors such as infective agents should be recorded.

CG1.12a Demonstration of certain infective agents is a prerequisite for some WHO lymphoma classification entities. For example, positive human T-lymphotrophic virus (HTLV) 1 serology is a prerequisite for the WHO entity adult T-cell leukaemia/lymphoma (ATLL). Other infective agents are associated with increased rates of certain lymphoma subtypes and can be supportive of the diagnosis (eg the association of Epstein–Barr virus (EBV) with some cases of Hodgkin lymphoma, Burkitt lymphoma and extranodal NK/T-cell lymphoma, nasal type).

CG1.12b Examples of infective agents that may be associated with, or contribute to the development of, lymphoproliferative disease include: human immunodeficiency virus (HIV), EBV, HTLV1, human herpesvirus (HHV) 8, hepatitis C, *Helicobacter pylori,*and *Borrelia burgdorferi*.

Comment

G1.13 Any further clinical information not given above should be described

CG1.13a This narrative section should be used to indicate any other relevant clinical information, and the source of the information if different from the clinical request form (eg follow-up phone call with the treating clinician).

Surgical handling

S1.05 Where lymphoma is suspected, the specimen must be sent immediately, intact and unfixed in a closed sterile container to the anatomical pathology laboratory.

CS1.05a Specimens may be transported at room temperature for up to two hours. For delays of 2–24 hours, specimens for flow cytometry studies should be kept sterile at room temperature in Hanks or RPMI 1640 solution.

Whilst interphase FISH can be performed on fixed, paraffin embedded tissue, other techniques including conventional cytogenetics and metaphase FISH require rapid transport of fresh, viable cells to the laboratory for short term culture and metaphase production. For optimal results, a piece of lymph node should be transported in sterile RPMI 1640 to the cytogenetics laboratory as soon as possible after excision. Cultures are usually only successful if set up on same day as specimen was collected[5]

Immunofluorescence transport medium containing ammonium sulfate is not suitable.

CS1.05b Biopsies should only be performed at a time and place where acceptable facilities for preparing the tissue for ancillary tests are available.[5]

2 Specimen handling and macroscopic findings

This chapter relates to the procedures required after the information has been handed over from the requesting clinician and the specimen has been received in the laboratory.

Tissue banking

G2.01 Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or research purposes. The decision to provide tissue should only be made when the pathologist is sure that the diagnostic process will not be compromised. As a safeguard, research use of the specimen may be put on hold until the diagnostic process is complete so that the specimen can be retrieved.

Specimen handling

G2.02 The unfixed specimen should be cut into 2-mm slices perpendicular to the long axis, using a fresh, sterile blade and the material distributed to the appropriate laboratories (internal and external).

CG2.02a Tissue distribution (or triage) may include frozen section, imprints, cytological cell block material, flow cytometry, paraffin sections, cytogenetics, molecular laboratory, microbiology laboratory, tissue bank, electron microscopy and macroscopic photography**.**

CG2.02b Well-prepared, formalin-fixed, paraffin-embedded sections remain the gold standard for lymph node diagnosis and are the highest priority of triage, usually elected from the central slices.

CG2.02c Material for ancillary studies may be selected from the ends, or poles of the lymph node where material is limited.

Specimen handling is documented in more detail elsewhere.[5]

Macroscopic findings

S2.01 The fluid in which the specimen is delivered to the laboratory must be reported.

CS2.01a Specimens may be received fresh or in solutions, including neutral buffered formalin, saline or transport medium. This information indicates what type of ancillary tests can be performed.

S2.02 Specimen handling or triage must be reported.

CS2.02a Specimen handling or triage information indicates the distribution of biopsy material to different laboratories (internal and/or external) and for different investigational modalities (see CG2.02a)

CS2.02b This provides a checklist to indicate how many and what sort of ancillary tests may have been performed on a specimen in which results are still pending. It also indicates what tissue samples may be available for any additional tests.

S2.03 The specimen type must be reported.

CS2.03a Examples include:

- peripheral blood
- aspirated fluid
- fine needle aspirate (FNA) biopsy
- needle core biopsy
- trephine biopsy
- endoscopic biopsy
- thoracoscopic biopsy
- laparoscopic biopsy
- punch biopsy
- incisional biopsy
- excisional biopsy
- resection (specify)
- other.

CS2.03b The type of biopsy indicates what tests may be possible on the sample and any likely limitations to diagnostic accuracy. When more than one biopsy has been performed on a patient, this identifies which biopsy the report refers to.

S2.04 The specimen size must be reported

CS2.04a The size of the specimen provides corroboration to the surgeon and other clinicians of the size and potential quality of the sample and any likely limitations to diagnostic accuracy.

CS2.04b Measurement is recommended in millimetres for incisional and excisional biopsies; gauge and length in millimetres for core biopsies; millilitres for fluids; and weight in grams for spleen.

G2.03 A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.

CG2.03a This is the traditional macroscopic description currently given in pathology reports.

CG2.03b To the extent that this information can be captured synoptically above, this component can be significantly reduced to describe only information not otherwise captured.

3 Microscopic findings

Microscopic findings relates to purely histological or cytological assessment. Information derived from multiple modalities is described in Chapter 5.

Chapter 3 is structured to allow reporting of the microscopic findings synoptically, by traditional narrative or by a combination of both. Depending upon case complexity and pathologist preference, G3.01 to G3.04 may be recorded on a synoptic report (by tick box) or by free text narrative. In cases where a synoptic style is unable to convey complex information or nuance, communication may be best achieved by a combination of synoptic information and traditional narrative.

For example, diffuse large B-cell lymphoma, follicular lymphoma and other monomorphous lymphomas constitute a majority of those encountered in western societies and may be described effectively and efficiently by using a structured checklist (see chapter 6).

S3.01 Microscopic findings must be recorded.

CS3.01a A description of the microscopic findings is important for clinical governance to indicate the process of diagnostic decision making and any areas of uncertainty. In complex or unusual cases, this is especially important. In a straightforward case, such as a follicular lymphoma or diffuse lymphoma, a few descriptors may be all that is required.

CS3.01b The description should include the following items (G3.01 to G3.05).

Abnormal cells

G3.01 The pattern of infiltration or architecture of abnormal cells should be reported.

CG3.01a The pattern of lymphomatous infiltration determines the tumour architecture in any given organ and has been an intrinsic part of all lymphoma classifications including the current WHO system. Follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma are all examples in which the architecture has helped to define the disease entity and can provide important diagnostic information.

CG3.01b Descriptors for architectural patterns may vary depending on the organ involved. In secondary lymphoid organs, such as lymph nodes, descriptors may include:

- diffuse
- follicular
- marginal zone
- mantle zone
- sinusoidal
- paracortical.

In bone marrow, descriptors may include:

- paratrabecular
- interstitial
- diffuse.

In cutaneous infiltrates, descriptors may include:

- epidermotropic
- band-like
- perivascular
- periadnexal
- nodular
- diffuse
- wedge-shaped
- superficial
- deep.

Descriptors for other distinctive patterns of infiltration that may have predictive value for the diagnosis include:

- angiocentric and/or angiodestructive
- panniculitis-like
- intravascular
- presence of lymphoepithelial lesions
- presence of proliferation centres.

G3.02 The size of abnormal cells should be reported.

CG3.02a Tumour cell size has been an important element since the beginning of lymphoma classification. It was once a defining criterion for earlier morphological classifications such as the Working Formulation.[32] With the advent of immunophenotyping, and clinicopathological (REAL and WHO) classifications,[2,33] size is no longer paramount but it remains an integral and important part of the overall diagnostic picture for any given lymphoma. Most WHO entities comprise lymphoma cells of a characteristic size and this element may be essential in corroborating the diagnostic subtype.

CG3.02b Tumour cell size is not clearly defined in the WHO publication.[2]

The table below represents a longstanding consensus definition.

Descriptor	**Size related to histiocyte or TBM (tingible body macrophage) nucleus**
Small	< histiocyte nucleus
Medium	= histiocyte nucleus
Large	> histiocyte nucleus

CG3.02c Cell size may be recorded as:

- small
- medium
- large
- mixed
- indeterminate

G3.03 The cytomorphology of abnormal cells should be reported.

CG3.03a Cytomorphology refers to characteristic cytological features of individual tumour cells. Certain lymphomas, or groups of lymphomas, have characteristic cytomorphological features that may be an important clue to the specific lymphoma subtype.

CG3.03b There are many descriptors, each of which can be found in the relevant section of the WHO publication (2008).[2] These include generic as well as specific variants that are strongly associated to a particular lymphoma subtype. Examples are shown below.

- Generic descriptors:
  - pleomorphic, hyperlobate, anaplastic, clear cell, giant cell, spindle cell, signet ring cell, blastic or indeterminate
- Specific descriptors:
  - centroblastic, centrocytic, immunoblastic, plasmacytic, lymphoplasmacytic, lymphoplasmacytoid, prolymphocytic, paraimmunoblastic, plasmablastic, monocytoid, centrocyte-like, popcorn cell, Reed-Sternberg cell-like, etc.

G3.04 Proliferative indicators of abnormal cells should be recorded.

CG3.04a The following observations may assist in assigning grade to the lymphoma or be part of diagnostic criteria (eg for Burkitt lymphoma, WHO 2008[2]states 'nearly 100% of cells are positive for Ki67') or supportive morphologic criteria (eg subcutaneous panniculitis-like T-cell lymphoma, demonstrates abundant background apoptotic debris)

For example:

- tumour cell apoptosis
- mitotic index
- proliferative index (using Ki-67 immunostain)

S3.02 The grade (for follicular lymphoma) must be reported.

CS3.02a WHO (2008) criteria are used.[2] This edition of the WHO classification states that it is acceptable to place Grades 1 and 2 together as Grade 1–2 (low grade).

Grade	Definition[a]
1	0–5 centroblasts per hpf
2	6–15 centroblasts per hpf
3	> 15 centroblasts per hpf
3a	centrocytes present

3b	solid sheets of centroblasts

hpf = high-power field
a These counts are based on a field area of 0.159 mm^2

CS3.02b Primary cutaneous follicle centre lymphoma should not be graded

CS3.02c WHO 2008 (page 220)[2] states:
'If diffuse areas of any size comprised predominantly or entirely of large blastic cells, are present in any case of follicular lymphoma, a diagnosis of diffuse large B-cell lymphoma is also made'.

Host cells

G3.05 Host cells and tissue reactions should be reported.

CG3.05a Certain subtypes of lymphoma are associated with characteristic reactive infiltrates and tissue reactions. This may be important in defining the specific subtype of lymphoma and the likely clinical effects.

For example, the absence of an associated eosinophilic or neutrophilic infiltrate in classical lymphocyte-rich Hodgkin lymphoma helps to distinguish it from other forms of classical Hodgkin lymphoma. Certain subtypes of NHL are defined by the reactive cellular milieu such as 'T-cell and histiocyte-rich variant of diffuse large B-cell lymphoma'.

CG3.05b Typical descriptors for host cell reactions include:

- eosinophil-rich
- T-cell-rich
- histiocyte-rich
- neutrophil-rich
- plasma cell-rich
- erythrophagocytic

CG3.05c Typical descriptors for host tissue reactions include:

- necrotic
- sclerotic
- granulomatous
- suppurative
- high endothelial venule hyperplasia
- follicular dendritic cell proliferation.

Comment

G3.06 A narrative description should be reported as required.

CG3.06a Use of this free text section is at the discretion of the reporting pathologist.

It may be left blank or used in addition to structured elements as a way of clarifying or modulating that information. At the discretion of the reporting pathologist it may be used as a traditional microscopic description. In this circumstance, items G3.01 to G3.04 can be used as a checklist to ensure a complete dataset.

CG3.06b Information which could be recorded here in addition to the above includes:

- correlation of microscopic findings with the proposed diagnosis
- commentary on factors affecting morphological assessment (eg tissue preservation, size of sample, sample type (eg FNA versus core biopsy versus open biopsy)[5] adequacy of cellularity for a cytology sample).

4 Ancillary study findings

An ancillary study is any pathology investigation which may form part of a cancer pathology report but which is not a part of routine histological assessment. Ancillary studies may be used to determine lineage, clonality or disease classification or subclassification; as prognostic biomarkers; or to indicate the likelihood of patient response to specific biological therapies.

Ancillary studies currently in diagnostic use for lymphoma include: flow cytometry, immunohistochemistry, cytogenetics and molecular studies. Other test modalities which may become important in the future should be reported using the same principles, standards and guidelines.

It is rarely necessary for all modalities to be used in a single case but it is a central tenet of the WHO classification that lineage determination is a prerequisite for diagnosis.[2] For this reason, evidence for lineage and clonality, where relevant, are standards and at least one of the ancillary test modalities will be required to achieve a diagnosis. The method used, however, will vary from one institution to another, from case to case and according to disease subtype.

S4.01 All ancillary studies which have been performed, and which are pending, must be reported.

CS4.01a Every case will have at least one form of ancillary investigation.

CS4.01b Lineage determination is a prerequisite for diagnosis. Proof of clonality may be required to establish a diagnosis of lymphoma and subtyping usually requires determination of an immunophenotypic profile. The particular choice of modality used may vary according to the institution, pathologist preference and tumour type

CS4.01c For each modality, the results are listed, or the report annotated as:

- not performed
- pending

G4.01 All multidisciplinary diagnostic findings should be integrated into the final report.

CG4.01a The anatomical pathology report is frequently the only complete record of all pathology investigations performed on the specimen and thus provides the treating clinician with a complete and integrated record of all relevant pathological investigations and conclusions.

G4.02 Each class of ancillary investigation should form a separate subsection under its own heading

S4.02 For ancillary studies performed in the reporting anatomical pathology laboratory (eg immunohistochemistry) test results and interpretation must be reported in full, including all positive, negative and indeterminate results.

G4.03 Relevant results derived from an external laboratory should, where possible, be reported verbatim, identifying the tissue substrate used, the source laboratory, laboratory episode number and reporting pathologist or scientist.

CG4.03a The test performance characteristic for the particular test and laboratory should be recorded.

G4.04 For each ancillary study heading used, information should be reported as much as possible as discrete items using checklists.

G4.05 Each modality should include facility for a narrative comment.

CG4.05a This allows free text expression for:

- interpretive comment
- comment on how the results correlate with the proffered diagnosis
- description of complex elements which are beyond synoptic capture

In cases where the investigation is performed in an external laboratory, this section is used to quote the interpretive comments or conclusion verbatim from the relevant laboratory, with the name of the reporting pathologist or scientist.

5 Synthesis and overview

Information that is synthesised from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here.

In haematological neoplasia, the tumour type, as defined by the WHO classification, is clinicopathological and is derived from a combination of clinical information, microscopic findings and at least some form of ancillary study.

Similarly, tumour stage is synthesised from multiple classes of information – clinical, macroscopic and microscopic.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the report 'Summary' or 'Diagnosis' section in the final formatted report.

Overarching case comment is synthesis in narrative format. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a cancer report is essential.

S5.01 Lineage must be reported

CS5.01a Lineage determination is a prerequisite for diagnosis. In cases of indeterminate diagnosis, this information may be important to a clinical understanding of the disease

CS5.01b Although lineage may be determined in many cases by a single ancillary study such as immunohistochemistry, there are occasions where the lineage is indicated by multiple observations (eg immunohistochemistry, flow cytometry and molecular studies). Since these findings may not necessarily be concordant, the final determination of lineage may require interpretation. Comment describing the diagnostic resolution of any discordance should be given in the narrative section below (**S5.04**).

CS5.01c Descriptors for lineage include:

- B-cell
- T-cell
- NK-cell
- NK/T-cell
- histiocytic
- dendritic cell
- myeloid
- monocytic
- myelomonocytic
- mast cell.

In classical Hodgkin lymphoma, the lineage may be best recorded as 'Hodgkin-like' or 'in keeping with Hodgkin lymphoma'.

Cases of indeterminate diagnosis may be of 'null', 'unknown' or 'unproven' lineage.

G5.01 Clonality should be reported.

CG5.01a Evidence of monoclonality may provide corroborative evidence for T-cell and B-cell lymphoma. In cases of uncertain diagnosis, the presence or absence of monoclonality may alter clinical management.

For certain other haemopoietic neoplasms, such as Hodgkin lymphoma, histiocytic and dendritic cell neoplasms, there are no readily available means of establishing clonality. In such cases, the absence of detectable T-cell or B-cell clonality by routine methods may be important in corroborating the diagnosis.

CG5.01b Although clonality may be determined in many cases by a single ancillary study such as immunohistochemistry, there are occasions where the clonality is indicated by multiple observations (for example, immunohistochemistry, flow cytometry and molecular studies). Since these findings may not necessarily be concordant, the final determination of clonality may require interpretation. Comment describing the diagnostic resolution of any discordance should be given in the narrative section below (**S5.04**).

CG5.01c Descriptors best used for clonality are:

- monoclonal
- polyclonal
- oligoclonal

In other circumstances 'unknown', 'untested' or 'unproven' should be recorded as it may be important for the clinician to be aware that monoclonality has not been proven.

CG5.01d Molecular tests should be performed by laboratories having the required expertise. For each molecular test, it is essential to know its limitations, sensitivity and specificity.[34] Ideally this should be recorded with each case. Sensitivity and specificity will vary with different techniques; for example, fluorescent in situ hybridisation (FISH) vs polymerase chain reaction (PCR) for t(11;14), and may vary with different tissue samples. The results of molecular tests should never be used in isolation. Clonality does not always equate with malignancy, nor does its absence necessarily indicate a benign process.

S5.02 The WHO disease subtype must be recorded

CS5.02a The specific WHO category is recorded whenever possible. A generic diagnosis may be appropriate in some cases. For example:

- B-cell NHL, not further specifiable
- atypical lymphoid proliferation

G5.02 The International Classification of Diseases code for cancer (ICD-O-3) should be reported.

CG5.02a The ICD-O-3 codes are provided in WHO 2008.[2]

G5.03 The 'Diagnostic summary' section of the final formatted report should include:

a. specimen type (**S2.03**)

b. tumour site and laterality (**S1.03**, **S1.04**)

c. WHO diagnosis (**S5.02**)

d. grade where relevant (**S3.02**)

G5.04 Stage should be recorded if known.

CG5.04a Use the AJCC/UICC *Cancer Staging Manual*, 7th edition, to report the stage of the lymphoma.[22]

CG5.04b Staging for haemopoietic neoplasms is based on the Ann Arbor system originally developed for Hodgkin lymphoma, rather than the TNM system used in other cancers.

Ocular adnexal lymphoma is an exception to the above rule and is staged by the TNM system.[22]

For multiple myeloma, the Durie-Salmon staging system is recommended by the AJCC.[22,35]

CG5.04c Staging is clinicopathological and requires knowledge of multiple imaging modalities (CT/PET/MRI) as well as clinical examination, results of laboratory tests and bone marrow examination. Examination of cerebrospinal fluid may also be required in cases at risk of central nervous system involvement.

The results of these examinations are rarely known at the time of primary histopathological diagnosis.

G5.05 A supplementary report (or equivalent) should be added to the pathology report if further diagnostic information is subsequently obtained.

S5.03 Facility for overall case comment must be provided

CS5.03a This free text narrative is to provide overarching case commentary, as required. This commentary is mandatory in cases where the diagnosis is not definitive or is in any way compromised.

CS5.03b The narrative may include:

- information which is unexpected, or too complex or nuanced for structured capture
- description of the decision making trail including resolution of any discordant findings
- in cases of diagnostic ambiguity or uncertainty:
- reason for uncertainty
- differential diagnoses
- pending investigations
- recommendations for further action; this may include
    - rebiopsy (indicating preferred modality)[5]
    - specific investigations (eg imaging of specific area; specific viral serology)
    - referral of pathology material for second opinion; which should include detailed clinical history, imaging results, flow cytometry results and genetic results if known, all slides including H&Es and immunohistochemistry, unstained slides (10 or paraffin block)
- details of any second opinion sought.

6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. This provides a fully inclusive dataset for structured reporting of lymphoma. For emphasis, standards (mandatory elements) are formatted in bold font. The standards alone are equivalent to the 'minimum dataset' for lymphoma.

S6.01 The structured checklist provided may be modified as required but with the following restrictions:

a. All standards and their respective naming conventions, definitions and value lists must be adhered to.

b. Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.

G6.01 The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities.

CG6.01a Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow pathologist workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.

CG6.01b Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.

G6.02 Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply.

CG6.02a All extraneous information, tick boxes and unused values need to be deleted.

Clinical information and surgical handling

S1.01	**Patient name**	_____
	Date of birth	_____
	Sex	_____
	Identification and contact details of requesting doctor	_____
	Type of specimen	_____
	Date of request	_____
	Clinical information relevant to the investigations requested	_____ _____
G1.01	Patient identifiers (eg MRN, UHI, NHI)	_____ _____
G1.02	Pathology accession number	_____
S1.02	**Principal clinician**	_____
S1.03	**Site of biopsy:**	
	Lymph node (specify)	___
	Other (specify)	___
S1.04	**Laterality:**	
	Left	___
	Midline	___
	Right	___
	Unknown	___
G1.03	Reason for biopsy	_____
G1.04	Clinical or differential diagnosis	_____
G1.05	Involved sites or pattern of disease spread:	
	Nodal/Lymphatic	___
	Extranodal/Extralymphatic	___
	Nodal/Extranodal	___

Unknown ___

G1.06 Stage or clinical extent of disease

Solitary ___

Localised ___

Generalised ___

Unknown ___

G1.07 Constitutional symptoms

Present ___

Absent ___

Unknown ___

G1.08 Relevant laboratory test results _____

G1.09 Previous lymphoma or leukaemia diagnosis _____

Relevant previous biopsies:

Date of biopsy ___

Site of biopsy ___

Type of biopsy ___

Laboratory ___

Laboratory reference numbers ___

G1.10 Previous treatment _____

G1.11 Predisposing factors—Immuno-compromised states and auto immune conditions _____

G1.12 Predisposing factors—Infective agents _____

G1.13 Further clinical information

_____

_____

_____

Macroscopic findings

S2.01 Fluid specimen in which delivered to the laboratory _____

S2.02 **Specimen handling or triage** _____

S2.03 **Specimen type** _____

S2.04 **Specimen size:**

Biopsies (mm) ___

Fluid (mL) ___

Spleen (g) ___

G2.03 Narrative or macroscopic description _____

_____

_____

Microscopic findings

G3.01 Abnormal cells: patterns of infiltration or architecture: _____

G3.02 Abnormal cell size:

Small ___

Medium ___

Large ___

Mixed ___

Indeterminant ___

G3.03 Abnormal cell cytomorphology _____

G3.04 Abnormal cell proliferative indicators _____

S3.02 **Grade (follicular lymphoma):**

1 ___

2 ___

3 ___ **3a**___ **3b** ___

G3.05 Host cells and tissue reactions _____

G3.06 Narrative or microscopic description _____

_____

_____

Ancillary test findings

G4.03 Immunohistochemistry

S4.01 **Performed** ___

Not performed ___

S4.02 **Positive** _____

Negative _____

Equivocal _____

G4.05 Narrative interpretive comment _____

_____

_____

G4.03 Flow Studies

S4.01 **Performed** ___

Not performed ___

S4.02 **Positive** _____

Negative _____

Equivocal _____

G4.05 Narrative interpretive comment _____

_____

_____

G4.03 Other Test(s) (Iterative)

Test Result Type _____

Result _____

G4.05 Narrative interpretive comment _____

_____

_____

Synthesis and Overview

S5.01 **Lineage** _____

G5.01 Clonality _____

S5.02	**WHO disease subtype**	_____
G5.02	ICD-O-3 code	_____
G5.03	Diagnostic summary	_____ _____ _____
G5.04	Stage (AJCC/UICC 7th edition)	___
S5.03	**Overall case comment**	_____ _____ _____

7 Formatting of pathology reports

Good formatting of the pathology report is essential for optimising communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists' workflow as a priority.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer. For guidance on formatting pathology reports, please refer to Appendix 2.

Appendix 1 Pathology request form for lymphoma

S1.01	**Patient name**	_____
	Date of birth	_____
	Sex	_____
	Identification and contact details of requesting doctor	_____
	Type of specimen	_____
	Date of request	_____
	Clinical information relevant to the investigations requested	_____ _____
G1.01	Patient identifiers (eg MRN, UHI, NHI)	_____ _____
S1.02	**Principal clinician**	_____
S1.03	**Site of biopsy:**	
	Lymph node (specify)	___
	Other (specify)	___
S1.04	**Laterality:**	
	Left	___
	Midline	___
	Right	___
	Unknown	___
G1.03	Reason for biopsy	_____
G1.04	Clinical or differential diagnosis	_____
G1.05	Involved sites or pattern of disease spread:	
	Nodal/Lymphatic	___
	Extranodal/Extralymphatic	___
	Nodal/Extranodal	___
	Unknown	___

G1.06 Stage or clinical extent of disease

Solitary ___

Localised ___

Generalised ___

Unknown ___

G1.07 Constitutional symptoms

Present ___

Absent ___

Unknown ___

G1.08 Relevant laboratory test results

_____

G1.09 Previous lymphoma or leukaemia diagnosis

_____

Relevant previous biopsies:

Date of biopsy ___

Site of biopsy ___

Type of biopsy ___

Laboratory ___

Laboratory reference numbers ___

G1.10 Previous treatment

_____

G1.11 Predisposing factors—Immuno-compromised states and auto immune conditions

_____

G1.12 Predisposing factors—Infective agents

_____

G1.13 Further clinical information

_____

_____

_____

Appendix 2 Guidelines for formatting of a pathology report

Layout

Headings and spaces should be used to indicate subsections of the report, and heading hierarchies should be used where the LIS allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

Grouping like data elements under headings and using 'white space' assists in rapid transfer of information.[36]

Descriptive titles and headings should be consistent across the protocol, checklist and report. When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time.

Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or 'clutter'.

Within any given subsection, information density should be optimised to assist in data assimilation and recall. The following strategies should be used:

- Configure reports in such a way that data elements are 'chunked' into a single unit to help improve recall for the clinician.[36]
- Reduce 'clutter' to a minimum.[36] Thus, information that is not part of the protocol (eg billing information or Snomed codes) should not appear on the reports or should be minimised.
- Reduce the use of formatting elements (eg bold, underlining or use of footnotes) because these increase clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to mutate or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost
- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print
- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting
- supplementary reports may merge into the initial report.

Appendix 3 Example of a pathology report

Bush, George W.
C/O Paradise Close
Guantanamo Bay Resort
CUBA

Male

DOB 1/7/1998
MRN FMC1096785

Lab Ref: **09/P28460**
Referred: 30/2/2009

Managing Clinician: Dr G. Mengels
Rainforest Cancer Centre.
46 Smith Road,
Woop Woop, 3478

Referred by: Mr V. Putin
Suite 3, AJC Medical Centre,
Bunyip Crescent
Nar Nar Goon West, 3182

LYMPHOMA STRUCTURED REPORT

Diagnostic Summary

Excision biopsy of left cervical lymph node:

Follicular lymphoma, Grade 3a , paediatric variant (see comment)

Comment: Follicular lymphoma is uncommon at this age but the morphology is characteristic. Bcl-2 negativity is a frequent finding in this variant of follicular lymphoma and therefore has no bearing on the diagnosis. The morphological impression is supported by the PCR results in which a monoclonal IgH rearrangement was detected in triplicate samples.

The prognosis of Follicular lymphoma in pediatric patients appears to be good.

Supporting Information

CLINICAL

Site and laterality:	Left cervical lymph node
Presentation:	8 months history of lymphadenopathy
Indication for biopsy:	Diagnostic
Clinical impression:	? lymphoma
Disease extent:	Solitary
Other sites of disease:	Nil known
Const. symptoms:	Nil
Medical history:	None relevant
Predisposing factors:	Nil known

SPECIMEN

Type:	Excision biopsy
Size:	24 x 30mm
Received in:	Formalin
Triage:	Imprints, Paraffin sections, Flow cytometry, Cytogenetics, Molecular lab
Description:	Uniform pale gray cut surface. No necrosis.

MICROSCOPIC

Pattern of infiltration:	Follicular
Cell size:	Large
Cytomorphology:	Centrocytic, centroblastic
Tissue reactions:	Not applicable
Description:	The infiltrate is entirely follicular, consisting of admixed centrocytes and centroblasts with >15 centroblasts per hpf. No diffuse areas are identified. The tissue is well preserved and the morphology is entirely in keeping with the diagnosis.

Supporting Information (cont.)

Grade: By standard grading methods, this is a Grade 3a lymphoma however the value of grading in paediatric follicular lymphoma has not been established

IMMUNOPHENOTYPING

Immunohistochemistry:

Positive for: CD20, CD79a, bcl-6, bcl-10
Negative for: CD3, CD5, bcl-2, MUM1

Comment: The abnormal cells are clearly CD20 and CD79a positive B-cells. Stains for CD21 and CD35 confirm the presence of Follicular Dendritic Cells forming follicular structures throughout. Bcl-2 is clearly negative.

Flow cytometry:

Positive for: CD19, 20, CD10
Negative for: CD2, CD3, CD4, CD8, CD56, CD138, surface kappa and lambda light chains

Comment: "Phenotype is of a surface light chain negative B-cell population expressing CD10. There is no T-cell immunophenotypic aberrancy. Lack of expression of surface immunoglobulin light chains may be seen in a small percentage of B-cell lymphoma." Reported by Dr P. Merlin, Baudin Medical Centre.

CYTOGENETICS

Classical cytogenetics: Not performed
FISH: Not performed

MOLECULAR

PCR

IgH: Clonal rearrangement detected
TCRgamma: Polyclonal

Comment: "Monoclonal IgH gene rearrangement detected in gel electrophoresis. Genescan performed in triplicate confirms monoclonality – size 70bp +/- 1bp. suggesting lymphoproliferative disease of B lineage. This result should be interpreted in conjunction with clinical and laboratory findings." Reported by Ms Lesley Spell and Dr Sam Pikes
Test performed on fresh tumour tissue at Department of Tumour Genetics, Baudin Medical Centre.

SYNTHESIS

Lineage: B-cell (by flow cytometry, PCR and immunohistochemistry)
Clonality: Monoclonal (by PCR)
Diagnosis (WHO): Follicular lymphoma, paediatric variant; Grade 3a
ICD0-3: 9690/3
Stage: Unknown –not yet determined
Comment: See Diagnostic Summary section

Reported by Dr Samuel Wilks Authorised 4/3/2009

Appendix 4 Classification of haemopoietic neoplasia

WHO classification of haemopoietic neoplasia 2008[2].

Precursor lymphoid neoplasms

- B lymphoblastic leukemia/lymphoma, NOS
- B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
- B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged
- B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1* (*ETV6-RUNX1*)
- B lymphoblastic leukemia/lymphoma with hyperdiploidy
- B lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*
- B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1* (*TCF3-PBX1*
- T lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

- **Chronic lymphocytic leukemia/small lymphocytic lymphoma**
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
- *Splenic diffuse red pulp small B-cell lymphoma*
- *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
- *Pediatric follicular lymphoma*
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system
- Primary cutaneous DLBCL, leg type
- *EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma

- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman Disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Mature T- and NK-cell neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV-positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4-positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- *Anaplastic large cell lymphoma, ALK-negative*

Hodgkin lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- *Fibroblastic reticular cell tumor*
- *Indeterminate dendritic cell tumor*
- Disseminated juvenile xanthogranuloma

Post-transplant lymphoproliferative disorders (PTLD)

- Early lesions:
  - Plasmacytic hyperplasia

  - Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma type PTLD

Notes:
NOS = not otherwise specified
Italics = provisional entities in the 2008 WHO classification
For other abbreviations not defined above, see page 6 of this protocol.

Appendix 5 Staging

AJCC/UICC staging for Hodgkin and non-Hodgkin lymphomas[22,26]

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

Stage I	Involvement of a single lymphatic site (ie nodal region, Waldeyer's ring, thymus or spleen)(I),;or localised involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE)[a,b] Rare in Hodgkin lymphoma
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localised involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE) [b,c] The number of regions involved may be indicated by an Arabic numeral, as in, for example, II3.
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S)[b,c,d] Splenic involvement is designated by the letter S.
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid.[b,c,d]

[a] Multifocal involvement of a single extralymphatic organ is classified as stage IE and not stage IV.

[b] For all stages, tumour bulk greater than 10 to 15 cm is an unfavourable prognostic factor.

[c] The number of lymph node regions involved may be indicated by a subscript: eg, II_3. For stages II to IV, involvement of more than 2 sites is an unfavourable prognostic factor.

[d] For stages III to IV, a large mediastinal mass is an unfavourable prognostic factor.

Note: Direct spread of a lymphoma into adjacent tissues or organs does not influence classification of stage.

Appendix 6 Prognostic indicies

International Prognostic Index[37]

One point is assigned for each of the following risk factors:

- age greater than 60 years
- Stage III or IV disease
- elevated serum LDH
- ECOG/Zubrod performance status of 2, 3, or 4
- more than 1 extranodal site.

The sum of these points correlates with the following risk groups:

- low risk (0–1 points) —5-year survival of 73%
- low-intermediate risk (2 points) — 5-year survival of 51%
- high-intermediate risk (3 points) — 5-year survival of 43%
- high risk (4-5 points) — 5-year survival of 26%.

Follicular Lymphoma International Prognostic Index (FLIPI)[24]

One point is assigned for each of the following adverse prognostic factors:

- age greater than 60 years
- Stage III or IV disease
- greater than 4 lymph node groups involved
- serum haemoglobin less than 12 g/dL
- elevated serum LDH.

The sum of the points allotted correlates with the following risk groups:

- low risk (0-1 points) — 5 and 10-year survivals of 91% and 71%, respectively
- intermediate risk (2 points) — 5 and 10-year survivals of 78% and 51%, respectively
- high risk (3-5 points) — 5 and 10-year survivals of 53% and 36%, respectively.

Mantle Cell Lymphoma International Prognostic Index (MIPI)[38]

The point values are assigned as follows:

0 points	Age less than 50 years, ECOG performance status of 0-1, LDH less than 0.67 of the upper limit of normal, or white blood cell count (WBC) of less than 6700 cells/microlitre.
1 point	Age 50-59, LDH 0.67-0.99 of the upper limit of normal, or WBC 6700 to 9999 cells/microlitre.
2 points	Age 60-69, ECOG performance status of 2-4, LDH 1-1.49 times the upper limit of normal, or WBC 10,000-14,000 cells/microlitre.
3 points	Age 70 or greater, LDH 1.5 times the upper limit of normal or greater, and WBC of 15,000 cells/microlitre or greater.

The sum of the allotted points correlates with the following risk groups:

- low risk (0-3 points) — median survival not yet reached
- intermediate risk (4-5 points) — median survival of 51 months
- high risk (6-11 points) — median survival of 29 months.

References

1 AIHW (Australian Institute of Health and Welfare) and AACR (Australasian Association of Cancer Registries) (2007). *Cancer in Australia: an overview, 2006*. Cancer Series No. 37 (AIHW cat. no. CAN 32). AIHW, Canberra.

2 Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, Thiele J and Vardiman J (eds) (2008). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, IARC, Lyon.

3 McDermid I (ed) (2005). *Cancer Incidence Projections, Australia 2002 to 2011*, AIHW (Australian Institute of Health and Welfare) and AACR (Australasian Association of Cancer Registries), Canberra.

4 Horner M, Ries L, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse S, Feuer E, Huang L, Mariotto A, Miller B, Lewis D, Eisner M, Stinchcomb D and Edwards B (eds) (2009). *SEER Cancer Statistics Review, 1975–2006*, National Cancer Institute, Bethesda, Maryland.

5 Australian Cancer Network Diagnosis and Management of Lymphoma Guidelines Working Party (2005). *Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma*. Cancer Council Australia and Australian Cancer Network, Sydney.

6 Zarbo RJ (1992). Interinstitutional assessment of colorectal carcinoma surgical pathology report adequacy. A College of American Pathologists Q-Probes study of practice patterns from 532 laboratories and 15,940 reports. *Archives of Pathology and Laboratory Medicine* 116(11):1113-1119.

7 Leslie K and Rosai J (1994). Standardization of the surgical pathology report: formats, templates, and synoptic reports. *Seminars in Diagnostic Pathology* 11(4):253–257.

8 Kempson RL (1992). The time is now. Checklists for surgical pathology reports. *Archives of Pathology and Laboratory Medicine* 116(11):1107–1108.

9 Australian Cancer Network Colorectal Cancer Guidelines Revision Committee (2005). *Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*. The Cancer Council Australia and Australian Cancer Network, Sydney.

10 Maughan NJ, Morris E, Forman D and Quirke P (2007). The validity of the Royal College of Pathologists' colorectal cancer minimum dataset within a population. *British Journal of Cancer* 97(10):1393–1398.

11 Jaffe ES, Banks PM, Nathwani B, Said J and Swerdlow SH (2004). Recommendations for the reporting of lymphoid neoplasms: a report from the Association of Directors of Anatomic and Surgical Pathology. *Modern Pathology* 17(1):131–135.

12 CAP (College of American Pathologists) (2009). *Cancer protocols and checklists* Available from: <http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Fcancer%2Fcancer_protocols%2Fprotocols_index.html&_state=maximized&_pageLabel=cntvwr > (Accessed 13 October 2009).

13 Chan NG, Duggal A, Weir MM and Driman DK (2008). Pathological reporting of colorectal cancer specimens: a retrospective survey in an academic Canadian pathology department. *Canadian Journal of Surgery* 51(4):284–288.

14 Gill AJ, Johns AL, Eckstein R, Samra JS, Kaufman A, Chang DK, Merrett ND, Cosman PH, Smith RC, Biankin AV and Kench JG (2009). Synoptic reporting improves histopathological assessment of pancreatic resection specimens. *Pathology* 41(2):161–167.

15 Hammond EH and Flinner RL (1997). Clinically relevant breast cancer reporting: using process measures to improve anatomic pathology reporting. *Archives of Pathology and Laboratory Medicine* 121(11):1171–1175.

16 Harvey JM, Sterrett GF, McEvoy S, Fritschi L, Jamrozik K, Ingram D, Joseph D, Dewar J and Byrne MJ (2005). Pathology reporting of breast cancer: trends in 1989-1999, following the introduction of mammographic screening in Western Australia. *Pathology* 37(5):341–346.

17 HHS (Department of Health and Human Services), CDC (Centers for Disease Control and Prevention) and NCCDPHP (National Center for Chronic Disease Prevention and Health Promotion) (2005). *Report on the Reporting Pathology Protocols for Colon and Rectum Cancers Project*, HHS, CDC and NCCDPHP, Atlanta, Georgia.

18 Epstein JI, Srigley J, Grignon D and Humphrey P (2007). Recommendations for the reporting of prostate carcinoma. *Human Pathology* 38(9):1305–1309.

19 Murari M and Pandey R (2006). A synoptic reporting system for bone marrow aspiration and core biopsy specimens. *Archives of Pathology and Laboratory Medicine* 130(12):1825–1829.

20 Mohanty S, Piccoli A, Devine L, Patel A, William G, Winters S, Becich M and Parwani A (2007). Synoptic tool for reporting of hematological and lymphoid neoplasms based on World Health Organization classification and College of American Pathologists checklist. *BMC Cancer* 7:144.

21 RCPA (Royal College of Pathologists of Australasia) (2009). *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols*. RCPA, Surry Hills, NSW.

22 Edge SE, Byrd DR, Carducci MA and Compton CA (eds) (2010). *AJCC Cancer Staging Manual 7th ed.*, New York, NY.: Springer.

23 RCPA (Royal College of Pathologists of Australasia) (2004). *Chain of Information Custody for the Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers*. RCPA, Surry Hills, NSW.

24 Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, Au WY, Bellei M, Brice P, Caballero D, Coiffier B, Conde-Garcia E, Doyen C, Federico M, Fisher RI, Garcia-Conde JF, Guglielmi C, Hagenbeek A, Haioun C, LeBlanc M, Lister AT, Lopez-Guillermo A, McLaughlin P, Milpied N, Morel P, Mounier N, Proctor SJ, Rohatiner A, Smith P, Soubeyran P, Tilly H, Vitolo U, Zinzani PL, Zucca E and Montserrat E (2004). Follicular lymphoma international prognostic index. *Blood* 104(5):1258–1265.

25 AJCC (American Joint Committee on Cancer) (2002). *AJCC Cancer Staging Manual, 6th edition*. Springer-Verlag, New York.

26 Sobin L, Gospodarowicz M, Wittekind C and International Union against Cancer (eds) (2009). *TNM Classification of Malignant Tumours*, Wiley-Blackwell, Chichester, UK and Hoboken, New Jersey.

27 Prescott RJ, Wells S, Bisset DL, Banerjee SS and Harris M (1995). Audit of tumour histopathology reviewed by a regional oncology centre. *Journal of Clinical Pathology* 48(3):245–249.

28 Karim RZ, van den Berg KS, Colman MH, McCarthy SW, Thompson JF and Scolyer RA (2008). The advantage of using a synoptic pathology report format for cutaneous melanoma. *Histopathology* 52(2):130–138.

29 RCP (Royal College of Pathologists) (2009). *Datasets and tissue pathways* RCP Available from: <http://www.rcpath.org/index.asp?PageID=254> (Accessed 13th Oct 09).

30 Hermans J, Krol AD, van Groningen K, Kluin PM, Kluin-Nelemans JC, Kramer MH, Noordijk EM, Ong F and Wijermans PW (1995). International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. *Blood* 86(4):1460–1463.

31 Ekstrom Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, Spinelli JJ, La Vecchia C, Zheng T, Becker N, De Sanjose S, Chiu BC, Dal Maso L, Cocco P, Maynadie M, Foretova L, Staines A, Brennan P, Davis S, Severson R, Cerhan JR, Breen EC, Birmann B, Grulich AE and Cozen W (2008). Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 111(8):4029–4038.

32 National Cancer Institute (1982). National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. *Cancer* 49(10):2112–2135.

33 Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC and et al. (1994). A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 84(5):1361–1392.

34 Spagnolo DV, Ellis DW, Juneja S, Leong AS, Miliauskas J, Norris DL and Turner J (2004). The role of molecular studies in lymphoma diagnosis: a review. *Pathology* 36(1):19–44.

35 Durie BG and Salmon SE (1975). A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 36(3):842–854.

36 Valenstein PN (2008). Formatting pathology reports: applying four design principles to improve communication and patient safety. *Archives of Pathology and Laboratory Medicine* 132(1):84–94.

37 International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993). A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *New England Journal of Medicine* 329(14):987–994.

38 Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, Pfreundschuh M, Reiser M, Metzner B, Einsele H, Peter N, Jung W, Wormann B, Ludwig WD, Duhrsen U, Eimermacher H, Wandt H, Hasford J, Hiddemann W and Unterhalt M (2008). A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood* 111(2):558–565.