

# Lymphoma: The Cancer Collage

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When considering the term *lymphoma* in the realm of cancer, it calls to mind the visual of a collage. By pure definition, a collage is “an assemblage of diverse elements.”

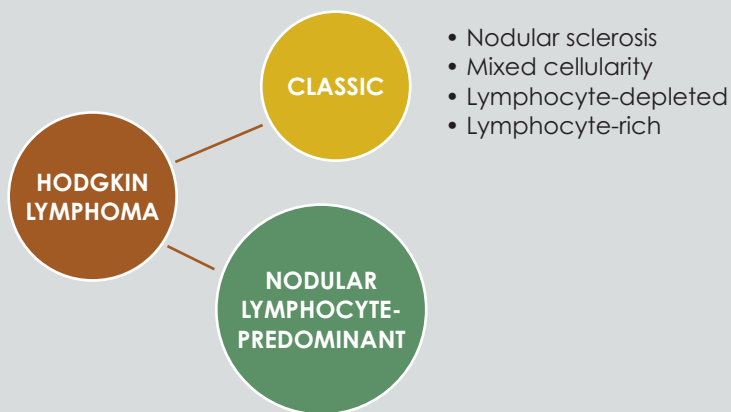
Lymphoma, as a hematologic malignancy of the lymphatic system, is a complex assemblage of different cellular histologies/entities, all of which follow a similar cellular “familiarity” in development. And, as can be common with collages, you may not be able to interpret the full extent of the vision without stepping back to consider all the particular elements – or in this case, the particular subtypes.

Cumulatively, when the impact of lymphomas is considered relative to incidence and prevalence, statistics from 2010 indicated that 628,415 people were living with lymphoma or were in remission, having no sign of the disease. This number included an approximate 153,535 people with Hodgkin lymphoma (HL) and 474,880 people with non-Hodgkin lymphoma (NHL).<sup>1</sup>

## HODGKIN LYMPHOMA: A CONTINUING THEME ON AN AGE-OLD DISEASE

Those of us around long enough remember when “Hodgkin’s disease” was the nomenclature used for this subtype of lymphoma. The reclassification to “Hodgkin lymphoma” confirmed its more appropriate alignment with lymphoma in terms of morphology and histology. One could say that HL is also a bit more straightforward related to subclassifications as compared with NHL. HL consists of two subtypes (classic and nodular lymphocyte-predominant), as graphically represented in Figure 1.

**Figure 1. Hodgkin Lymphoma Classification<sup>2</sup>**



### NON-HODGKIN LYMPHOMA

In contrast to Hodgkin lymphoma, NHL has many subtypes that add to the complexity. Historically, NHL has undergone several iterations of classification, based on the evolution in knowledge around cellular morphology and how these cells then align to specific histologic subtypes. To provide a review on changing perspectives around lymphomas, the following outlines some (but not all) of the particular classification systems that have been applied throughout the past half century.

A short history lesson on the changing classification of NHL: The 1950s and 1960s experienced the first attempt to organize the disease, with the development of the Rappaport system. This system classified the disease based on the “appearance” of cells, differentiating whether cells had diffuse or nodular characteristics.

Another significant classification change followed in the 1970s, when immunological concepts on the role of T and B cells in lymphoma were developed, with the result taking the form of several classification systems, such as the Working Formulation, Kiel system, and Lukes-Collins classification.

Yet another classification system was developed in 1994 – the Revised

European-American Lymphoma (REAL) classification. This system was devised with the objective of producing a unified classification for malignant lymphoma that included HL. The REAL classification listed lymphoma types as distinct biological entities/diseases that could be reliably diagnosed through histopathology. It separated peripheral and precursor cell lymphomas of both

B and T cell origin, and it applied to both nodal and extranodal lymphomas. The REAL classification was the first to truly acknowledge all the different subtypes of histologies present in lymphoma, which has subsequently allowed for the development of more targeted therapeutic options.

The most recent change came in 1995 when the REAL system was further revised by a working group within the World Health Organization (WHO). It became known as the WHO/REAL classification. Finally, in 2008, WHO updated a stand-alone classification for lymphomas (HL and NHL), which has been adopted by hematologists and is the reference point for subtype histological classification.<sup>3</sup>

Table 1 outlines the primary subtype entities of NHL, each potentially being subclassified by yet another level of histological definition and categorized under one of the two primary subtypes of NHL (either mature B-cell lymphomas or mature T-cell lymphomas).

**Table 1. Non-Hodgkin Lymphoma Subtypes and Histologies (with estimated incidence as a percent of total subtype)<sup>4</sup>**

B-cell lymphomas	Diffuse large B-cell lymphoma (31%)
	Follicular lymphoma (22%)
	Burkitt’s lymphoma (2.5%)
	Mucosa-associated lymphatic tissue (MALT) lymphoma (7.5%)
	Small-cell lymphocytic lymphoma – chronic lymphocytic leukemia (7%)
	Mantle cell lymphoma (6%)
	Mediastinal (thymic) large B-cell lymphoma (2.4%)
	Lymphoplasmacytic lymphoma – Waldenstrom macroglobulinemia (< 2%)
	Nodal marginal zone B-cell lymphoma (< 2%)
	Splenic marginal zone lymphoma (< 1%)
	Extranodal marginal zone B-cell lymphoma (< 1%)
	Intravascular large B-cell lymphoma (< 1%)
	Primary effusion lymphoma (< 1%)
Lymphomatoid granulomatosis (< 1%)	
T-cell and natural killer (NK) cell lymphoma (approximately 12% total)	T-cell and natural killer (NK) cell lymphoma (approximately 12% total)
T-cell and natural killer (NK) cell lymphoma (approximately 12% total)	Peripheral T-cell lymphoma, not otherwise specified
	Cutaneous T-cell lymphoma
	Anaplastic large-cell lymphoma
	Angioimmunoblastic T-cell lymphoma
	NK-cell lymphoma
Immunodeficiency-associated lymphoproliferative disorders	

Note: The percentages above for non-Hodgkin lymphoma (NHL) subtypes A and B are approximate and are provided to give a sense of the relative distribution of NHL subtypes. Immunodeficiency-associated lymphoproliferative disorders account for a very small percentage of total NHL cases.



The detail could go on, but whether it's HL or NHL, there is great variance in the number of new cases each year, all with relatively small patient populations. For instance, in 2010, the U.S. estimate of new cases of HL (across all subtypes) was 8,490.<sup>5</sup> Compare this with 65,540 new U.S. cases of NHL (again, all subtypes and histologies) in 2010.<sup>6</sup> When breaking down the incidence of NHL according to particular histologies, new cases become even more orphan/ultra-orphan in nature, such as only 3,932 estimated new cases of mantle cell lymphoma in 2010.<sup>7</sup>

#### MAKING SENSE OF REIMBURSEMENT WITHIN THE COMPLEXITY OF LYMPHOMAS

You as the reader may ask, "Why the lesson in lymphoma classifications?" Just in terms of diagnosis coding, there are more than 160 ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes to describe the various subtypes and lymph node involvement associated with different lymphomas. This therefore requires careful pathology interpretation, coupled with provider coding that most appropriately reflects the particular histology. Many times, if there is any question about histology, a not-otherwise-specified (NOS) miscellaneous-diagnosis

code may be designated. This creates further challenge for payors in determining consistent trends in lymphoma treatment via claims analysis.

Treatment options for lymphomas encompass a wide variety of drugs and biologics and stem cell transplantation, with patients possibly receiving multiple modalities based on the presentation of the disease. However, not all agents are necessarily applicable across the board for every lymphoma subtype or histology, a decision that can also be influenced by whether the lymphoma is considered indolent or aggressive in nature of development. This is yet another indication of the diversity of the morphology and histology of lymphomas, as well as the clinical trial design for individual agents.

Some of the standard chemotherapy agents employed in regimens include cyclophosphamide, doxorubicin, fludarabine, and mitoxantrone. However, the development of newer agents (both biologic and nonbiologic) has brought about improvement in patient outcomes, while reducing the adverse event profile for these patients. This includes agents such as Treanda (bendamustine), Rituxan (rituximab), Velcade (bortezomib), Arzerra (ofatumumab), Foltyn (pralatrexate), and the newest addition of Adcetris (brentuximab vedotin),

the first treatment for HL approved by the U.S. Food and Drug Administration (FDA) in more than 30 years.

Conventionally, the coverage decisions for the above-mentioned drugs and biologics focus on the FDA-approved indication, which may be only one specific lymphoma histology/entity, while others reflect expanded indications based on peer-reviewed published literature. Due to the cost associated with some of the newer drugs/biologics, prior authorization criteria or specialty pharmacy oversight may be in place. The bottom line is that these agents are not really dealt with differently than those for larger-volume cancers.

Despite the small patient population for lymphomas, a trend seen within certain payors is that of adding lymphomas to clinical pathway programs that may be in place. This pathway guidance may only be aligned with follicular or B-cell lymphomas, which are common forms of NHL, or those lymphoma histologies for which higher cost of care is associated.

So perhaps the lymphoma collage becomes a bit clearer in view. Although it has a basis of similarity in formative cellular structure, it is associated with distinct differences in morphology and histology that are associated with a legion of diagnosis codes. The final, and most important, vision is that there is a wide variety of effective treatment options making a difference in patient care.

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7. Based on the estimates of incidence presented in Table 1.