



**AAVBC**

AMERICAN ACADEMY OF VALUE BASED CARE

# **Non-Hodgkin's Lymphoma Quick Reference Guide**

**2026**

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## 1 CLINICAL SNAPSHOT

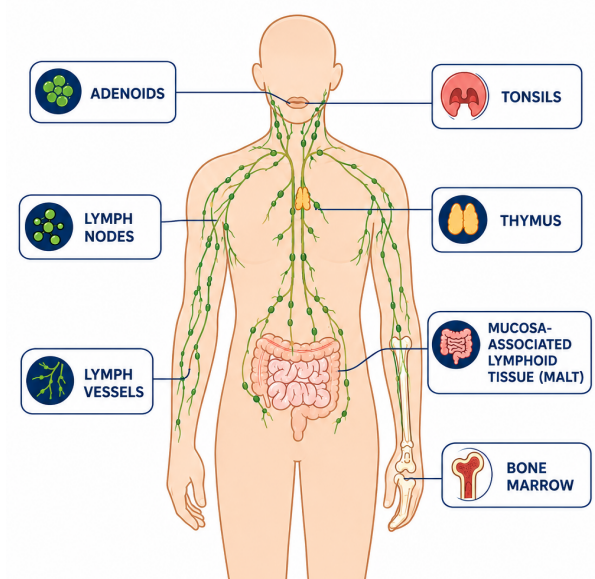
**Definition: Non-Hodgkin lymphoma (NHL)** is not a single disease but a heterogeneous group of more than **60** distinct lymphoid malignancies arising from **B-cell, T-cell, or NK-cell lymphocytes**, classified by the 2022 WHO/ICC framework into **indolent** and **aggressive** subtypes with widely divergent natural histories, treatment algorithms, and prognoses.<sup>1,2</sup> The most clinically important distinction for primary care is **indolent versus aggressive**: a patient with low-burden **follicular lymphoma** on active surveillance and a patient with **diffuse large B-cell lymphoma (DLBCL)** receiving curative-intent chemoimmunotherapy are not experiencing variations of one disease.<sup>2,3</sup> 'Indolent' **does not mean benign**: follicular lymphoma can undergo **histologic transformation** to DLBCL, a life-threatening event requiring urgent re-biopsy, code update, and treatment escalation; conversely, aggressive DLBCL is **potentially curable** with first-line therapy.<sup>1,3</sup>

### ICD-10 Codes:

NHL is reported across the **C82-C88** range, with three mandatory axes of specificity: histologic subtype, anatomic site (5th character), and disease status (active vs. **in remission**, suffix '**A**').<sup>4</sup> Follicular lymphoma is **C82.-** (grade I-IIIb plus site); small-cell B-cell lymphoma is **C83.0-**; mantle cell lymphoma is **C83.1-**; DLBCL is **C83.3-** (primary CNS lymphoma **C83.390**); mycosis fungoides is **C84.0-**, Sezary disease **C84.1-**, and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) **C84.4-**; extranodal marginal zone (MALT) lymphoma is **C88.4-.**<sup>4</sup> **C85.90** (NHL, unspecified, unspecified site) is a temporary placeholder for **pending pathology only** and must be updated to the confirmed subtype-and-site code.<sup>4</sup> Use **Z85.72** (personal history of NHL) only **after treatment is complete with no active surveillance.**<sup>4</sup>

**Prevalence and Burden:** The American Cancer Society estimates approximately **79,320** new NHL cases and **19,970** NHL-related deaths in the United States in 2026, with an overall 5-year relative survival near **74%** (ranging from **~88%** for **stage I** to **~64%** for **stage IV**).<sup>5</sup> NHL is strongly age-predisposed: more than **half** of all diagnoses occur in adults aged **65 or older**, the median age at DLBCL diagnosis is the **mid-60s** with roughly **30%** of patients older than **75**, and age-adjusted NHL incidence in adults aged 75–84 reaches approximately **110.9 per 100,000** versus **~19 per 100,000** in the overall population.<sup>3,5,6</sup> The **Global Burden of Disease 2021 analysis** estimated about **306,296** new cases and **158,813** deaths among adults ≥65 worldwide, a burden that is rising.<sup>7,8</sup> This makes NHL one of the **most clinically significant cancers older adults.**<sup>7</sup>

## Common Sites of Origin



## HCC/RAF V28 Mapping

| ICD-10 CODE(S) <sup>4</sup>                                  | HCC CATEGORY (V28) <sup>9</sup>                            | RAF (CNA) <sup>*10</sup> | DOCUMENTATION REQUIREMENT <sup>4</sup>                                                                                                                                                                                   |
|--------------------------------------------------------------|------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>C91.10-C91.19 Chronic lymphocytic leukemia (CLL/ SLL)</b> | <b>HCC 22</b> Bladder/ Colorectal and <b>Other Cancers</b> | 0.363                    | <b>Same biologic entity as SLL</b> ; coded <b>C91.1-</b> ( <b>NOT</b> an NHL C-code); <b>document:</b> Rai/Binet stage and treatment status; Richter transformation to DLBCL → recode to <b>C83.3-</b> ( <b>HCC 20</b> ) |
| <b>C83.30-C83.39 Diffuse large B-cell lymphoma (DLBCL)</b>   | <b>HCC 20</b> Lung and Other Severe Cancers                | 1.136                    | Aggressive tier; <b>document:</b> subtype (e.g., GCB vs. ABC), site, stage, and treatment status; confirm by hematopathology                                                                                             |
| <b>C83.3A DLBCL (in remission)</b>                           | <b>HCC 20</b> Lung and Other Severe Cancers                | 1.136                    | <b>Document:</b> remission status confirmed by oncology (complete vs. partial), date of last treatment, and ongoing surveillance plan; do not use for active disease — recode to C83.3- if relapse documented            |
| <b>C82.00-C82.99 Follicular lymphoma</b>                     | <b>HCC 21</b> Lymphoma and Other Cancers                   | 0.671                    | <b>Most common indolent NHL</b> ; <b>document:</b> grade (1-3A vs. 3B), site(s), stage, and active treatment or watch-and-wait status with annual MEAT                                                                   |

| ICD-10 CODE(S) <sup>4</sup>                                                                   | HCC CATEGORY (V28) <sup>9</sup>                                                 | RAF (CNA)* <sup>10</sup> | DOCUMENTATION REQUIREMENT <sup>4</sup>                                                                                                                                                                        |
|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>C88.40–C88.49</b><br><b>Extranodal marginal zone lymphoma of MALT</b>                      | <b>HCC 21</b><br><b>Lymphoma</b> and Other Cancers                              | 0.671                    | <b>Document:</b> primary site (e.g., gastric, ocular), stage, and treatment status; specify "MALT lymphoma," not "lymphoma NOS"                                                                               |
| <b>C83.10–C83.19</b><br><b>Mantle cell lymphoma</b>                                           | <b>HCC 20</b> Lung and Other Severe Cancers                                     | 1.136                    | <b>Document:</b> subtype, site(s), stage, and Ki-67 if available; do not group with indolent disease                                                                                                          |
| <b>C83.1A</b> Mantel cell lymphoma (in remission)                                             | <b>HCC 21</b><br>Lymphoma and Other Cancers                                     | 0.671                    | <b>Document:</b> remission status confirmed by oncology (complete vs. partial), date of last treatment, and ongoing surveillance plan; do not use for active disease — recode to C83.1- if relapse documented |
| <b>C84.00–C84.09</b><br><b>Mycosis fungoides</b>                                              | <b>HCC 20</b> Lung and Other Severe Cancers                                     | 1.136                    | <b>Document:</b> TNMB stage, skin involvement, and treatment status; <b>distinguish from Sézary disease (C84.1-)</b>                                                                                          |
| <b>C84.10–C84.19</b><br><b>Sézary disease</b>                                                 | <b>HCC 17</b> Cancer Metastatic; AML Except Promyelocytic                       | 4.209                    | Aggressive T-cell lymphoma; <b>document:</b> blood involvement (circulating Sézary cells), skin staging, and <b>leukemic status</b> ; specify "Sézary disease," <b>not</b> "cutaneous lymphoma NOS"           |
| <b>C84.40–C84.49</b><br><b>Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)</b> | <b>HCC 19</b><br>Myelodysplastic Syndromes/ Multiple Myeloma/ and Other Cancers | 1.798                    | <b>Document:</b> T-cell phenotype confirmed by immunohistochemistry, subtype, site(s), and stage                                                                                                              |
| <b>C84.60–C84.69</b><br><b>Anaplastic large cell lymphoma (ALCL), ALK-positive</b>            | <b>HCC 20</b> Lung and Other Severe Cancers                                     | 1.136                    | <b>Document:</b> ALK status by immunohistochemistry, subtype, site, and stage                                                                                                                                 |
| <b>C83.00–C83.09</b><br><b>Small cell B-cell lymphoma</b>                                     | <b>HCC 21</b><br>Lymphoma and Other Cancers                                     | 0.671                    | <b>Document:</b> subtype, site, stage, and active status; distinguish from CLL/SLL ( <b>C91.1-</b> )                                                                                                          |
| <b>C85.90–C85.99</b><br><b>Non-Hodgkin lymphoma, unspecified</b>                              | <b>HCC 21</b><br>Lymphoma and Other Cancers                                     | 0.671                    | <b>AVOID</b> if pathology specifies subtype; <b>placeholder for pending pathology ONLY</b> ; overuse as a permanent code is the most common NHL coding error; query pathology/ oncology record                |

| ICD-10 CODE(S) <sup>4</sup>           | HCC CATEGORY (V28) <sup>9</sup> | RAF (CNA)* <sup>10</sup> | DOCUMENTATION REQUIREMENT <sup>4</sup>                                                                                                                                   |
|---------------------------------------|---------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Z85.72 Personal history of NHL</b> | No HCC                          | —                        | <b>AVOID</b> for active disease: use <b>ONLY after</b> oncology confirms treatment complete and active surveillance has ended; never use while monitoring active disease |

**ABBREVIATIONS:** ICD-10 = International Classification of Diseases, 10th Revision; HCC = Hierarchical Condition Category; RAF = Risk Adjustment Factor; CNA = Community Non-Dual Eligible, Aged segment; AML = acute myeloid leukemia; NOS = not otherwise specified; PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified; MDS = myelodysplastic syndrome; DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-cell; ABC = activated B-cell; TNMB = tumor/node/metastasis/blood; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; NHL = non-Hodgkin lymphoma; MEAT = Monitor, Evaluate, Assess, Treat; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; MALT = mucosa-associated lymphoid tissue; CMS = Centers for Medicare & Medicaid Services; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification

\*RAF values represent the Community Non-Dual Eligible Aged (CNA) coefficient from the 2026 CMS-HCC model;<sup>10</sup> values vary across patient populations based on eligibility and care setting

### Risk-Adjusted Care Resources per Patient/Year<sup>9,10</sup>

Risk-adjusted care resource allocation — MA base rate (~\$10,402.34) × RAF coefficient

**SÉZARY DISEASE**  
**\$43.8K**

HCC 17 · RAF 4.209

**CLL/SLL**  
**\$3.8K**

HCC 22 · RAF 0.363



### AAVBC PERSPECTIVE

*From the AAVBC's perspective, value-based care in non-Hodgkin's lymphoma requires replacing a "wait-and-see" approach with accountable diagnostic stewardship that prioritizes early tissue diagnosis, recognizing that NHL frequently mimics benign disease and **often presents extranodally**.<sup>11</sup> Persistent lymphadenopathy or chronic, treatment-refractory presentations (including unexplained gastrointestinal, cutaneous, or neurologic symptoms) with or without B symptoms should trigger an **urgent suspected lymphoma pathway** rather than repeated empiric therapy or prolonged observation, with explicit documentation of "suspected lymphoma → urgent hematology referral" and a goal of initiating diagnostic workup **within 14 days**.<sup>12</sup> Definitive diagnosis requires **excisional lymph node biopsy whenever feasible**, with tissue reviewed by an experienced hematopathologist rather than reliance on fine-needle aspiration alone.<sup>1,13</sup>*

*The PCP's role extends well beyond diagnosis. Value is created through **active shared-care with hematology** by preventing avoidable complications, **including**: febrile neutropenia, tumor lysis syndrome, polypharmacy toxicity, steroid-induced hyperglycemia, and unnecessary emergency visits. Equally important is **coordinating treatment-informed survivorship care** and **long-term monitoring** for therapy-related cardiovascular disease, secondary malignancies, infection risk, and other late effects.<sup>14,15</sup> This positions primary care*

as an **accountable co-manager throughout the NHL care continuum** rather than a passive referrer.<sup>15</sup>

## 2 RECOGNITION AND DIAGNOSIS

### Medicare Part B Covered Screenings and Surveillance (Adult and Geriatric)

There is no NHL-specific population-wide screening test; workup begins once clinical suspicion is established.<sup>1</sup> Coverage applies to diagnostic and staging workup, not screening. Medicare Part B covers the following diagnostic tests and workup **when medically necessary**:

| TEST/PROCEDURE                                        | FREQUENCY                                                                                | CPT/HCPCS                | CLINICAL INDICATION <sup>1,13,16,17</sup>                                                                                                               |
|-------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Excisional lymph node biopsy</b>                   | <b>At diagnosis</b> ; the diagnostic standard                                            | 38500/38510 /38525       | <b>Suspected NHL</b> ; FNA alone is <b>insufficient</b> for diagnosis; preserves architecture for grading                                               |
| <b>Core needle biopsy (± FNA + ancillary studies)</b> | <b>At diagnosis</b> ; anatomically inaccessible nodes only, with expert pathology review | 38505                    | Acceptable alternative only with immunohistochemistry, flow cytometry, molecular analysis, and FISH; <b>multiple cores preferred</b>                    |
| <b>Flow cytometry/immunophenotyping</b>               | On the diagnostic specimen                                                               | 88184/88185 /88187/88188 | Establishes <b>lineage</b> and <b>subtype</b> (e.g., CD20, CD5, CD10, cyclin D1); required <b>before</b> subtype-specific coding                        |
| <b>FDG-PET/CT (staging/restaging)†</b>                | <b>At staging</b> ; end-of-induction response assessment (Deauville score)               | 78814/78816              | <b>Standard for FDG-avid lymphomas</b> under Lugano classification; CT alone for non-avid histologies (marginal zone, CLL/SLL)                          |
| <b>Hepatitis B serology</b>                           | <b>ONCE before</b> any rituximab/anti-CD20 therapy = <b>mandatory</b>                    | —                        | HBsAg, anti-HBc, anti-HBs; PCPs can complete this <b>before referral</b> to prevent fatal reactivation                                                  |
| <b>Echocardiogram or MUGA</b>                         | <b>ONCE before</b> anthracycline-based therapy                                           | —                        | <b>Baseline LVEF guides regimen selection</b> ; document LVEF <b>before</b> doxorubicin (R-CHOP); guides anthracycline-free regimens in cardiac disease |



| TEST/PROCEDURE                            | FREQUENCY                                                       | CPT/HCPCS                                   | CLINICAL INDICATION <sup>1,13,16,17</sup>                                                                                                                           |
|-------------------------------------------|-----------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Comprehensive Geriatric Assessment</b> | <b>Before treatment</b> in older adults with tolerance concerns | 99483 (cognitive)/<br>G0438-<br>G0439 (AWV) | ADL/IADL, Mini-Cog, nutrition, polypharmacy, comorbidity; G-8, VES-13, CARG/CRASH tools <b>guide treatment intensity</b>                                            |
| <b>Advance Care Planning (AWV)†</b>       | <b>At diagnosis</b> in frail/elderly + when goals change        | 99497/99498                                 | <b>Document:</b> directives, surrogate, code status; NHL diagnosis is an appropriate trigger when comorbidities or advanced age shape treatment intensity decisions |

**ABBREVIATIONS:** CPT/HCPCS = Current Procedural Terminology/Healthcare Common Procedure Coding System; NHL = non-Hodgkin lymphoma; FNA = fine-needle aspiration; FISH = fluorescence in situ hybridization; FDG = fluorodeoxyglucose; PET/CT = positron emission tomography/computed tomography; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; PCP = primary care provider; MUGA = multigated acquisition scan; LVEF = left ventricular ejection fraction; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ADL = activities of daily living; IADL = instrumental activities of daily living; CARG = Cancer and Aging Research Group; CRASH = Chemotherapy Risk Assessment Scale for High-Age Patients; VES-13 = Vulnerable Elders Survey-13; AWV = Annual Wellness Visit; ACP = advance care planning; CMS = Centers for Medicare & Medicaid Services; NCD = National Coverage Determination; LCD = Local Coverage Determination; CGA = Comprehensive Geriatric Assessment

† CMS covers FDG-PET for staging, restaging, and treatment monitoring of lymphoma under NCD 220.6

Coverage includes up to 3 post-therapy PET/CT scans per patient per tumor type; additional scans require LCD-level medical necessity justification

‡ ACP is covered with no patient copay when performed during the AWV; 99497 covers the first 30 minutes, 99498 each additional 30 minutes



## CLINICAL PEARL: PATTERN RECOGNITION- HODGKIN VS. NON-HODGKIN LYMPHOMA IN OLDER ADULTS

**NHL and HL cannot be distinguished clinically;** both require excisional biopsy with immunohistochemistry.<sup>1,18</sup> However, **presentation patterns** can guide suspicion and referral urgency.<sup>19,20</sup>

**NHL is far more common in older adults** (median diagnosis ~67 years) and more often presents with generalized, **noncontiguous lymphadenopathy** and **extranodal involvement** (GI tract, skin, bone marrow, CNS).<sup>21</sup> **Indolent subtypes** (e.g., follicular, marginal zone) may wax and wane over months; aggressive subtypes (e.g., DLBCL) present with rapidly enlarging masses, elevated LDH, and B symptoms. Mediastinal disease is less common than in HL.<sup>22</sup>

HL **spreads predictably node-to-node** and classically presents with localized cervical/supraclavicular adenopathy plus a mediastinal mass (>50% of cases).<sup>18,22</sup> In older adults, HL's second incidence peak (ages **50-70**) involves **mixed-cellularity and EBV-positive subtypes** with advanced disease and B symptoms — **mimicking aggressive NHL**.<sup>23,24</sup>

**Bottom line:** Diffuse adenopathy with extranodal sites **favours NHL**; localized upper-body adenopathy with a mediastinal mass **raises HL suspicion**.<sup>18,19</sup> Both require **excisional biopsy**, not FNA: Reed-Sternberg cells (HL) and NHL subtyping both depend on **intact tissue architecture**.<sup>1,18</sup>



## Subtle Early Signs in Older Adults (>65)

| SIGN/SYMPTOM <sup>19,23,25,26</sup>                                                                                                                                                                                            | CLINICAL SIGNIFICANCE <sup>1,20,27,28</sup>                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Firm, rubbery, mobile, painless lymph node &gt;1 cm not regressing within 4 weeks</b>                                                                                                                                       | The <b>classic lymphoma node</b> ; should not be dismissed as reactive; nodes >2 cm, hard, fixed, or matted carry <b>higher malignancy risk</b> and warrant excisional biopsy           |
| <b>Supraclavicular or epitrochlear lymphadenopathy of any duration</b>                                                                                                                                                         | These locations carry the <b>highest malignancy signal</b> ; check beyond the cervical chain → supraclavicular, axillary, epitrochlear, and inguinal nodes are <b>frequently missed</b> |
| <b>B-symptoms: fever &gt;38°C, drenching night sweats, &gt;10% weight loss over 6 months</b>                                                                                                                                   | Constitutional symptoms suggest an <b>aggressive subtype</b> and require expedited evaluation, not routine scheduling                                                                   |
| <b>Persistent extranodal symptoms unresponsive to standard therapy</b>                                                                                                                                                         | Gastric MALT (epigastric pain mimicking <i>H. pylori</i> gastritis), cutaneous lymphoma (eczema-like lesions), or splenomegaly may be <b>lymphoma presenting outside the nodes</b>      |
| <b>Disproportionate growth of one node, rising LDH, or new B-symptoms in a known indolent lymphoma</b>                                                                                                                         | Suggests <b>histologic transformation</b> (or Richter transformation in CLL) to aggressive disease; re-biopsy and <b>urgent oncology contact</b>                                        |
| <b>Fatigue, weight loss, or night sweats attributed to existing comorbidities</b>                                                                                                                                              | In multimorbid elderly patients these are too readily ascribed to CHF, COPD, or diabetes, driving emergency-route diagnosis (OR 1.56-1.80)                                              |
| <b>Unexplained cytopenias with or without lymphadenopathy</b>                                                                                                                                                                  | Anemia, thrombocytopenia, or leukopenia <b>may reflect marrow involvement</b> ; <b>pursue workup</b> rather than isolated symptomatic treatment                                         |
| <b>Persistent pruritus or skin lesions unresponsive to dermatologic treatment</b>                                                                                                                                              | Consider <b>cutaneous T-cell lymphoma</b> (mycosis fungoides), routinely misdiagnosed as psoriasis, contact dermatitis, or fungal infection                                             |
| <b>ABBREVIATIONS:</b> MALT = mucosa-associated lymphoid tissue; LDH = lactate dehydrogenase; CLL = chronic lymphocytic leukemia; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; OR = odds ratio |                                                                                                                                                                                         |

## Geriatric Risk Factors

| FACTOR                                                               | RISK SIGNAL                                                                                              | NOTES                                                                                                     |
|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Immunosuppression (HIV, transplant, primary immunodeficiency)</b> | RR <b>15</b> (low-grade) to <b>400</b> (high-grade NHL) in HIV vs. general population <sup>1,29,30</sup> | The strongest single risk category; loss of immune surveillance drives lymphomagenesis <sup>1,29,30</sup> |

| FACTOR                                                  | RISK SIGNAL                                                                                                                           | NOTES                                                                                                                 |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Autoimmune disease (RA, Sjögren, SLE)</b>            | <b>Increased risk</b> ; magnitude varies by subtype <sup>31</sup>                                                                     | Chronic <b>antigenic/inflammatory drive</b> ; Sjögren is strongly linked to parotid/MALT lymphoma <sup>32</sup>       |
| <b>Adult-onset diabetes mellitus (after age 30)</b>     | RR <b>2.18</b> (95% CI 1.22-3.90); RR <b>2.90</b> for ≥15 years' duration <sup>33</sup>                                               | Iowa Women's Health Study (women 55-69) → among the most directly <b>elderly-relevant estimates</b> <sup>33</sup>     |
| <b>Chronic infections (H. pylori, EBV, hepatitis C)</b> | <b>Causal for gastric MALT</b> ( <i>H. pylori</i> ); <b>EBV</b> → Burkitt and NK/T-cell; HCV → splenic MZL and DLBCL <sup>11,34</sup> | <i>H. pylori</i> eradication can <b>induce remission</b> of localized gastric MALT lymphoma <sup>1,34,35</sup>        |
| <b>Prior blood transfusion</b>                          | RR <b>1.95</b> (95% CI 1.33-2.85) <sup>33</sup>                                                                                       | Observed in older women; mechanism likely <b>immune modulation</b> <sup>33</sup>                                      |
| <b>Obesity</b>                                          | Risk factor specifically for <b>DLBCL</b> <sup>36</sup>                                                                               | A <b>modifiable factor</b> ; also affects chemotherapy dosing and tolerance <sup>11</sup>                             |
| <b>Cigarette smoking</b>                                | Association with <b>follicular lymphoma</b> in pooled analyses <sup>11</sup>                                                          | The most actionable modifiable exposure; <b>counsel cessation</b> <sup>37</sup>                                       |
| <b>History of prior cancer</b>                          | RR <b>1.92</b> (95% CI 1.21-3.06) <sup>33</sup>                                                                                       | Survivors warrant <b>continued surveillance</b> ; secondary-malignancy risk is elevated <sup>38</sup>                 |
| <b>Older age (peak risk ~age 80)</b>                    | Incidence ~ <b>59.2 per 100,000</b> at ≥65 (global) <sup>8</sup>                                                                      | <b>More than half</b> of NHL is diagnosed at <b>≥65</b> ; the dominant epidemiologic driver in Medicare <sup>39</sup> |

**ABBREVIATIONS:** RR = relative risk; NHL = non-Hodgkin lymphoma; HIV = human immunodeficiency virus; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; MALT = mucosa-associated lymphoid tissue; CI = confidence interval; EBV = Epstein-Barr virus; HCV = hepatitis C virus; MZL = marginal zone lymphoma; DLBCL = diffuse large B-cell lymphoma

## Diagnostic Thresholds (Lugano Staging and Risk Stratification)

**NHL diagnosis follows a stepwise sequence:** clinical suspicion (persistent lymphadenopathy, extranodal symptoms, B symptoms, or incidental imaging finding), excisional lymph node biopsy with immunohistochemistry and flow cytometry to confirm subtype, laboratory workup, and imaging for staging.<sup>1,2,11,13</sup> NHL encompasses **>60 subtypes** ranging from **indolent** (follicular, marginal zone) to **aggressive** (DLBCL, mantle cell, Burkitt), each requiring subtype-specific

immunophenotyping: this is why **excisional biopsy** (not FNA) is the diagnostic standard.<sup>1,11,13</sup> Core needle biopsy is acceptable **only when excisional biopsy is not feasible**, provided multiple cores are obtained with IHC, flow cytometry, and molecular studies.

## Essential Workup

The standard workup **across NHL subtypes includes**:<sup>1,13,40</sup>

- **CBC** with differential, comprehensive metabolic panel, LDH
- **Hepatitis B serology** (HBsAg, anti-HBc) = mandatory **before** any anti-CD20 therapy (e.g., rituximab) to prevent **fatal reactivation**
- **PET/CT for FDG-avid lymphomas** (DLBCL, FL, MCL); CT alone for non-avid histologies (marginal zone, CLL/SLL)
- **Echocardiogram** if anthracycline-based therapy (e.g., R-CHOP) is planned
- Bone marrow biopsy is **no longer routinely required for DLBCL** when PET/CT is performed, but remains **useful for indolent lymphomas**

**PCPs can expedite the diagnostic pathway** by ordering the initial labs (CBC, CMP, LDH, hepatitis B serology) and **referring for excisional biopsy before the oncology appointment**.

## Staging: Lugano Classification (2014)

NHL uses the same Lugano classification as HL, with one key difference: the A/B suffix for constitutional symptoms is not used in NHL staging.<sup>1,13</sup> For treatment purposes, stages **I-II** are considered **limited** and stages **III-IV** are **advanced**.<sup>1</sup> PET-CT determines extent for **FDG-avid lymphomas**; CT is sufficient for non-avid subtypes.<sup>1,13</sup>

| STAGE      | DEFINITION                                                         |
|------------|--------------------------------------------------------------------|
| <b>I</b>   | One nodal region or one extranodal site                            |
| <b>II</b>  | ≥2 nodal regions, same side of diaphragm                           |
| <b>III</b> | Nodal regions on both sides of diaphragm                           |
| <b>IV</b>  | Disseminated extralymphatic involvement (liver, lung, bone marrow) |

## Risk Stratification: Key Prognostic Indices

Unlike HL (which uses a **single IPS for advanced disease**), NHL uses **subtype-specific prognostic scores**.<sup>1,2,11</sup> PCPs do not need to calculate these, but understanding them helps **contextualize oncology communications**.

### International Prognostic Index (IPI) — used for DLBCL and aggressive NHL

| IPI FACTOR (1 POINT EACH) | THRESHOLD |
|---------------------------|-----------|
| <b>Age</b>                | >60 years |
| <b>Serum LDH</b>          | >ULN      |

| IPI FACTOR (1 POINT EACH)                                                                                                                                                                                   |  | THRESHOLD |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-----------|
| ECOG performance status                                                                                                                                                                                     |  | ≥2        |
| Ann Arbor Stage                                                                                                                                                                                             |  | III-IV    |
| Extranodal sites                                                                                                                                                                                            |  | >1        |
| Risk groups: low (0-1), low-intermediate (2), high-intermediate (3), high (4-5). The NCCN-IPI refines this with weighted age and LDH categories for better discrimination in the rituximab era <sup>1</sup> |  |           |

**ABBREVIATIONS:** ECOG = Eastern Cooperative Oncology Group performance status

### Follicular Lymphoma International Prognostic Index (FLIPI)

**Five factors:** age >60, stage III-IV, hemoglobin <12 g/dL, LDH >ULN, >4 nodal sites. Three risk groups (low 0-1, intermediate 2, high ≥3).<sup>1,19</sup> Treatment initiation in FL is guided by the GELF criteria (tumor burden assessment), not FLIPI alone — many patients are appropriately managed with **active surveillance** ("watch and wait").<sup>1</sup>

### Mantle Cell Lymphoma International Prognostic Index (MIPI)

**Four factors:** age, ECOG, LDH, WBC. Three risk groups with 5-year OS of **83%** (low), **63%** (intermediate), **34%** (high).<sup>41,42</sup> **TP53 mutation status** is an additional critical prognostic marker.<sup>43</sup>

### Response Assessment: Deauville 5-Point Scale

**The Deauville scale** standardizes PET/CT interpretation at **end-of-treatment** and drives all PET-adapted treatment decisions.<sup>1,44</sup>

| SCORE    |    | FDG PET/CT SCAN RESULT                                                              |
|----------|----|-------------------------------------------------------------------------------------|
| Negative | 1  | No uptake                                                                           |
| Negative | 2  | Uptake ≤ mediastinum                                                                |
| Negative | 3  | Uptake > mediastinum but ≤ liver                                                    |
| Positive | 4  | Uptake moderately higher than liver and visually above adjacent background activity |
| Positive | 5  | Uptake markedly higher than liver and/or new lesions                                |
| Positive | X* | New areas of uptake unlikely to be related to lymphoma                              |

**ABBREVIATIONS:** CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography

**\*Watchful waiting, biopsy, or additional imaging tests may be appropriate depending on clinical circumstances**



## CLINICAL PEARL - COMPREHENSIVE GERIATRIC ASSESSMENT TO GUIDE THERAPY INTENSITY IN NHL

**More than half of NHL is diagnosed at age  $\geq 65$ .**<sup>45</sup> Both the NCCN Older Adult Oncology Guidelines and ASCO guidelines recommend geriatric assessment (GA) in **all older patients with cancer** to identify vulnerabilities not captured by routine evaluation.<sup>17,46</sup>

**The GA evaluates** functional status (ADL/IADL), comorbidity, cognition, nutrition, polypharmacy, and mobility/falls.<sup>46</sup> The **G-8** (score  $\leq 14$  triggers full GA) and **VES-13** (score  $\geq 3$  indicates vulnerability) are recommended screening tools;<sup>46,47</sup> **CARG** and **CRASH** tools further guide treatment intensity.<sup>17</sup>

**Fitness classification directly determines treatment approach:** **fit patients** may receive full-dose chemoimmunotherapy (e.g., R-CHOP), **unfit patients** attenuated regimens (e.g., R-mini-CHOP), and **frail patients** palliative or novel-agent approaches.<sup>45</sup> A study of 105 older adults with **aggressive NHL** validated the VES-13 as **significantly associated with:** grade  $\geq 3$  toxicity, unplanned hospitalization, and 1-year mortality (100% sensitivity).<sup>48</sup> Proactive multidisciplinary management (geriatrics, cardiology, primary care) is recommended.<sup>46</sup>

## Summary of Staging and Assessment Tools

| SYSTEM                                    | PURPOSE                                 | PCP RELEVANCE                                                    |
|-------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| <b>Lugano (2014)</b> <sup>13</sup>        | Anatomic staging (I-IV)                 | <b>Same system as HL;</b> no A/B suffix for NHL                  |
| <b>IPI</b> <sup>49</sup>                  | DLBCL/aggressive NHL prognosis          | <b>5 simple factors;</b> helps interpret oncology notes          |
| <b>FLIPI</b> <sup>50</sup>                | Follicular lymphoma prognosis           | Guides <b>watch-and-wait vs. treatment decisions</b>             |
| <b>MIPI</b> <sup>41</sup>                 | Mantle cell lymphoma prognosis          | Age, ECOG, LDH, WBC; TP53 status critical                        |
| <b>Deauville 5-PS</b> <sup>13</sup>       | PET response assessment                 | Scores <b>1-3</b> = adequate; <b>4-5</b> = inadequate            |
| <b>Geriatric Assessment</b> <sup>17</sup> | Fitness classification (age $\geq 65$ ) | G-8 $\leq 14$ or VES-13 $\geq 3$ <b>triggers full assessment</b> |

**ABBREVIATIONS:** HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; IPI = International Prognostic Index; DLBCL = diffuse large B-cell lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; MIPI = Mantle Cell Lymphoma International Prognostic Index; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; WBC = white blood cell count; 5-PS = 5-point scale; PET = positron emission tomography; VES-13 = Vulnerable Elders Survey-13

## Clues to Dig Deeper

| CLINICAL CLUE                                                                          | WHY IT MATTERS                                                                                                                                                   | NEXT DIAGNOSTIC STEP                                                                                                 |
|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| <b>Lymphadenopathy persisting beyond 4 weeks</b>                                       | The single highest-yield PCP behavior change is to <b>shorten diagnostic delay</b> rather than re-treat empirically <sup>12,51</sup>                             | Excisional lymph node biopsy with hematopathology review; <b>do not rely on FNA</b> <sup>1,12</sup>                  |
| <b>Persistent extranodal symptoms (GI, skin, CNS) refractory to standard treatment</b> | One-third of NHL is <b>extranodal</b> and is the most frequently miscoded; chronic refractory presentations should raise <b>lymphoma suspicion</b> <sup>11</sup> | Biopsy the involved site with immunophenotyping; <i>H. pylori</i> testing for gastric MALT <sup>34,35</sup>          |
| <b>Single rapidly enlarging node or rising LDH in known indolent lymphoma</b>          | Signals <b>histologic</b> (or <b>Richter</b> ) <b>transformation</b> to aggressive disease → update code and treatment-escalation trigger <sup>1,52</sup>        | <b>Re-biopsy the discordant site</b> ; urgent oncology contact; update ICD-10 on confirmation <sup>1</sup>           |
| <b>CD5+ small B-cell neoplasm called 'CLL' without cyclin D1 testing</b>               | Mantle cell lymphoma <b>mimics CLL</b> but needs intensive therapy; misclassification has high clinical stakes <sup>43,53</sup>                                  | Request <b>cyclin D1/t(11;14) FISH</b> (and SOX11 if cyclin D1–) <b>before</b> accepting a CLL label <sup>1,54</sup> |
| <b>Lymph-node specimen read as 'reactive hyperplasia' that does not resolve</b>        | Follicular lymphoma and AITL are routinely <b>misread as benign hyperplasia</b> early in disease <sup>55</sup>                                                   | Request <b>expert hematopathology consultation</b> and ensure full immunophenotyping/molecular testing <sup>1</sup>  |
| <b>Unexplained splenomegaly or cytopenias</b>                                          | May reflect splenic <b>marginal zone lymphoma</b> or marrow involvement <sup>1,34</sup>                                                                          | CBC, peripheral smear, imaging; <b>hematology referral</b> for marrow evaluation <sup>26</sup>                       |
| <b>Symptoms attributed to age or comorbidity in a multimorbid elder</b>                | Diagnostic anchoring delays NHL recognition and raises emergency-route diagnosis <sup>26</sup>                                                                   | Re-examine all nodal basins and spleen; pursue biopsy when a node is persistent or atypical <sup>2,56</sup>          |

**ABBREVIATIONS:** PCP = primary care physician; FNA = fine-needle aspiration; NHL = non-Hodgkin lymphoma; GI = gastrointestinal; CNS = central nervous system; MALT = mucosa-associated lymphoid tissue; LDH = lactate dehydrogenase; ICD-10 = International Classification of Diseases, 10th Revision; CLL = chronic lymphocytic leukemia; FISH = fluorescence in situ hybridization; AITL = angioimmunoblastic T-cell lymphoma; CBC = complete blood count

## Common Oversights

| OVERSIGHT/SHORTCUT <sup>1,12,55,56</sup>                                                                                                                                                                                                                       | WHY IT MATTERS — WHAT TO DO INSTEAD <sup>1,11,26,57</sup>                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Relying on FNA for the initial lymphoma diagnosis</b>                                                                                                                                                                                                       | FNA cannot assess architecture or grade and is insufficient per NCCN; obtain an <b>excisional biopsy</b> reviewed by a hematopathologist                                      |
| <b>Prescribing empiric corticosteroids for unexplained lymphadenopathy</b>                                                                                                                                                                                     | Steroids <b>lyse lymphoma cells</b> and mask histology, causing false-negative biopsies; <b>avoid them until lymphoma is excluded</b>                                         |
| <b>Interpreting waxing-and-waning nodes as resolved infection</b>                                                                                                                                                                                              | Indolent lymphoma nodes <b>naturally fluctuate</b> ; track size and dates, and biopsy a node persisting beyond 4 weeks rather than re-treating                                |
| <b>Accepting a 'CLL' label on a CD5+ neoplasm without cyclin D1</b>                                                                                                                                                                                            | Mantle cell lymphoma <b>masquerades as CLL</b> but is aggressive; request cyclin D1/t(11; <sup>14</sup> ) <b>before</b> treatment is chosen                                   |
| <b>Treating 'NHL' as one disease with one regimen</b>                                                                                                                                                                                                          | More than 60 subtypes have <b>distinct trajectories</b> ; indolent disease may be actively monitored while aggressive DLBCL is curative-intent → <b>confirm subtype first</b> |
| <b>Missing histologic/Richter transformation in known indolent disease</b>                                                                                                                                                                                     | A single growing node, rising LDH, or new B-symptoms warrant <b>re-biopsy and urgent escalation</b> , not continued surveillance                                              |
| <b>Examining only the cervical chain</b>                                                                                                                                                                                                                       | Supraclavicular (highest malignancy signal), axillary, epitrochlear, and inguinal nodes plus splenomegaly are <b>commonly missed</b> → palpate all basins                     |
| <b>Ascribing B-symptoms and fatigue to existing comorbidities</b>                                                                                                                                                                                              | Diagnostic anchoring in multimorbid elders <b>delays diagnosis</b> and worsens the route to care; <b>keep lymphoma on the differential</b>                                    |
| <b>Equating 'watch and wait' with doing nothing</b>                                                                                                                                                                                                            | <b>Active surveillance</b> is evidence-based for <b>low-burden indolent FL</b> ; schedule <b>structured monitoring visits</b> rather than discharging the patient             |
| <b>ABBREVIATIONS:</b> FNA = fine-needle aspiration; NCCN = National Comprehensive Cancer Network; CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; LDH = lactate dehydrogenase; FL = follicular lymphoma |                                                                                                                                                                               |



## Key Differentials in Elderly

| PRESENTATION                                                            | DIFFERENTIAL                                                                                                     | KEY TESTS                                                                                                                    |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| <b>Persistent generalized or localized lymphadenopathy</b>              | <b>Reactive/infectious lymphadenitis; NHL;</b> Hodgkin lymphoma; metastatic carcinoma; sarcoidosis <sup>12</sup> | <b>Excisional biopsy;</b> CBC, LDH; viral serologies; chest/abdomen/pelvis imaging <sup>1,12</sup>                           |
| <b>CD5+ small B-cell neoplasm</b>                                       | <b>CLL/SLL vs. mantle cell lymphoma</b> (both CD5+); marginal zone lymphoma <sup>1,34</sup>                      | Cyclin D1, t(11;14) FISH, SOX11; CD23/CD200; flow cytometry <sup>43,53</sup>                                                 |
| <b>Lymph node read as reactive follicular hyperplasia</b>               | Benign reactive hyperplasia vs. <b>follicular lymphoma</b> vs. <b>early AITL</b> <sup>55</sup>                   | BCL2 IHC, CD10, light-chain restriction; <b>expert hematopathology review</b> <sup>1,11</sup>                                |
| <b>Chronic gastric or GI symptoms</b>                                   | <i>H. pylori</i> gastritis/peptic ulcer disease vs. <b>gastric MALT lymphoma</b> or GI DLBCL <sup>1,34</sup>     | Endoscopy with adequate biopsies; <i>H. pylori</i> staining; FISH for MALT1; flow cytometry <sup>1,58</sup>                  |
| <b>Chronic refractory skin lesions</b>                                  | Eczema, psoriasis, dermatitis, fungal infection vs. <b>cutaneous T-cell or B-cell lymphoma</b> <sup>59,60</sup>  | Skin biopsy with T-cell clonality and <b>immunophenotyping</b> per NCCN cutaneous algorithm <sup>60,61</sup>                 |
| <b>Systemic symptoms with polyclonal hypergammaglobulinemia</b>         | Autoimmune disease or chronic infection vs. <b>angioimmunoblastic T-cell lymphoma</b> (AITL) <sup>55</sup>       | <b>Lymph node biopsy</b> with CD10+ T cells, expanded CD21+ follicular dendritic meshwork; T-cell clonality <sup>40,55</sup> |
| <b>New rapidly growing node + rising LDH in known indolent lymphoma</b> | Indolent progression vs. <b>histologic/ Richter transformation</b> to DLBCL <sup>1,53</sup>                      | <b>Re-biopsy the discordant site;</b> PET-CT; LDH; urgent oncology referral <sup>1,57</sup>                                  |

**ABBREVIATIONS:** NHL = non-Hodgkin lymphoma; CBC = complete blood count; LDH = lactate dehydrogenase; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; FISH = fluorescence in situ hybridization; AITL = angioimmunoblastic T-cell lymphoma; BCL2 = B-cell lymphoma 2; IHC = immunohistochemistry; GI = gastrointestinal; MALT = mucosa-associated lymphoid tissue; DLBCL = diffuse large B-cell lymphoma; NCCN = National Comprehensive Cancer Network; PET-CT = positron emission tomography-computed tomography

## Comorbidity Screening

| CONDITION                                | PRELEVANCE/ASSOCIATION* <sup>1,2,11,62</sup>                                                                                                   | SCREENING APPROACH* <sup>1</sup>                                                                                                                                          |
|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Cardiovascular disease/CHF</b>        | <b>Anthracycline</b> (doxorubicin) <b>cardiotoxicity</b> may preclude standard R-CHOP; LVEF <50% requires <b>regimen modification</b>          | <b>Baseline echocardiogram</b> or MUGA <b>before</b> anthracycline therapy; favor CDOP/CEOP/GCVP + rituximab in cardiac disease; document <b>I11.0/I50.-</b> when present |
| <b>Diabetes mellitus</b>                 | <b>Independent NHL risk factor</b> (RR 2.18); prednisone in CHOP causes significant hyperglycemia requiring active management                  | Intensify <b>glucose monitoring during steroid phases</b> ; coordinate insulin adjustments with oncology; document <b>E11.-</b>                                           |
| <b>Chronic kidney disease</b>            | <b>Alters clearance of:</b> methotrexate, lenalidomide, and other renally excreted agents; common in elderly NHL patients                      | Calculate CrCl <b>before</b> renally cleared agents; monitor renal function per cycle; adjust doses per FDA labels; document N18.- CKD stage                              |
| <b>Hepatitis B (chronic or resolved)</b> | Rituximab can trigger <b>fatal HBV reactivation</b> , including in anti-HBc+/HBsAg– patients (resolved infection)                              | <b>Mandatory</b> HBsAg, anti-HBc, anti-HBs <b>before any anti-CD20 therapy</b> ; antiviral prophylaxis when indicated; document <b>B18.-/Z22.51</b>                       |
| <b>Cognitive impairment</b>              | <b>Affects:</b> adherence, consent capacity, toxicity reporting, and delirium risk during treatment                                            | <b>Mini-Cog/MoCA screen</b> ; document <b>R41.-/F03.-</b> ; caregiver involvement; delirium-prevention protocols                                                          |
| <b>Malnutrition/hypoalbuminemia</b>      | Strongest modifiable predictor of <b>grade 3+ chemotoxicity</b> (OR 4.29) and <b>unplanned hospitalization</b> (OR 2.83) in older NHL patients | <b>Nutritional assessment before treatment</b> ; albumin as prognostic marker; <b>dietitian referral</b> ; document <b>E44.-/R63.4</b>                                    |
| <b>Polypharmacy</b>                      | <b>Drug-drug interactions with:</b> ibrutinib (CYP3A4), venetoclax, and lenalidomide; raises toxicity risk                                     | Medication reconciliation <b>every visit</b> ; Beers Criteria review; <b>GA-guided deprescribing</b> ; document <b>Z79.-</b>                                              |
| <b>VTE risk</b>                          | NHL is independently prothrombotic, <b>compounded by:</b> immobility, central lines, and certain agents (lenalidomide, L-asparaginase)         | <b>Risk-based thromboprophylaxis</b> ; vigilance for new limb swelling or dyspnea; document <b>Z86.718</b>                                                                |

| CONDITION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | PREVALENCE/ASSOCIATION* <sup>1,2,11,62</sup> | SCREENING APPROACH* <sup>1</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------|
| <b>ABBREVIATIONS:</b> CHF = congestive heart failure; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; NHL = non-Hodgkin lymphoma; RR = relative risk; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CDOP = cyclophosphamide, doxorubicin (liposomal), vincristine, prednisone; CEOP = cyclophosphamide, etoposide, vincristine, prednisone; GCVP = gemcitabine, cyclophosphamide, vincristine, prednisone; CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; MoCA = Montreal Cognitive Assessment; OR = odds ratio; CYP3A4 = cytochrome P450 3A4; GA = geriatric assessment; VTE = venous thromboembolism; CKD = chronic kidney disease<br><b>*Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions</b> |                                              |                                  |



## RED FLAG — EMERGENCY/ACTIVATE CRISIS RESPONSE

These emergency conditions require **immediate intervention** in patients with known or suspected non-Hodgkin lymphoma:

- **Superior vena cava (SVC) syndrome** (facial/upper extremity swelling, dyspnea, stridor with mediastinal mass):<sup>63,64</sup> in NHL, chemotherapy alone achieves **complete symptom relief in ~80% of cases**
  - → **Emergency CT angiography**; endovascular stenting for life-threatening symptoms; tissue diagnosis before chemotherapy when feasible
- **Tumor lysis syndrome** (hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, AKI):<sup>1</sup> highest risk in Burkitt and bulky DLBCL; may cause fatal arrhythmias and renal failure
  - → **Rigorous IV hydration**; rasburicase for high-risk (G6PD testing required); allopurinol for low/intermediate risk
- **Spinal cord compression** (new back pain with weakness, sensory change, or bladder dysfunction):<sup>65</sup> lymphoma is highly **radiosensitive** → primary RT preferred over surgery
  - → **Emergency MRI entire spine**; high-dose dexamethasone; radiation oncology consultation
- **Febrile neutropenia** (temp  $\geq 38.3^{\circ}\text{C}$  with ANC  $< 500/\text{mm}^3$ ):<sup>66</sup> empiric antibiotics within 1 hour of triage
  - → Blood cultures **before** antibiotics; anti-pseudomonal monotherapy (cefepime, meropenem, or piperacillin/tazobactam)
- **Airway compromise from rapidly enlarging cervical or mediastinal lymphadenopathy**<sup>67</sup>
  - → **Emergency airway management**; avoid sedation/supine positioning; urgent oncology consultation
- **Severe symptomatic hypercalcemia** (confusion, arrhythmias):<sup>68</sup> calcitriol-mediated mechanism in lymphoma makes glucocorticoids particularly effective
  - → IV saline hydration; IV zoledronic acid; calcitonin for rapid onset; glucocorticoids

**RED FLAG — URGENT (24-72 HOURS)**

Expedited workup required = **do not** refer to routine follow-up:

- **Rapidly enlarging lymphadenopathy with B symptoms, especially age >55:**<sup>67,69</sup> suggests aggressive subtype; avoid empiric corticosteroids, which mask histology
  - → Urgent hematology-oncology referral; do not complete an empiric antibiotic trial before referring
- **Suspected histologic or Richter transformation** = disproportionate growth of a single site, rising LDH, or new B symptoms in known indolent lymphoma<sup>1,53</sup>
  - → Same-day oncology contact; PET-CT; excisional biopsy of discordant lesion (SUV ≥5); update ICD-10 on confirmation
- **New neurologic symptoms in a known NHL patient** (headache, seizures, focal deficits) suggesting CNS involvement<sup>69,70</sup>
  - → **Urgent MRI brain ± spine**; lumbar puncture if safe; neurology and oncology consultation
- **Persistent lymphadenopathy >4 weeks**; supraclavicular or epitrochlear adenopathy of any duration; nodes >2 cm, hard, fixed, or matted<sup>67</sup>
  - → Expedited referral (within days, not routine); **excisional biopsy**, not FNA
- **Unexplained cytopenias or splenomegaly:**<sup>69</sup> may reflect marrow involvement or splenic MZL
  - → CBC, peripheral smear, imaging; hematology referral
- **Persistent skin lesions unresponsive to dermatologic treatment:**<sup>67</sup> consider cutaneous T-cell lymphoma
  - → Skin biopsy with T-cell clonality and immunophenotyping

### 3 MEAT DOCUMENTATION ESSENTIALS

NHL documentation translates a heterogeneous, subtype-defined malignancy into **a record that supports continuity, care coordination, and accurate risk adjustment.**<sup>4,9</sup> **The most frequent pitfalls:** leaving a patient on **C85.90** (NHL unspecified) after pathology confirms a subtype, failing to update the code after histologic or Richter transformation, dropping anatomic-site and remission-status specificity, and omitting comorbidities that drive treatment tolerance. The MEAT framework below ties **each element into appropriate clinical action:**

**Case vignette:** A 74-year-old male presents for follow-up. Excisional biopsy confirmed **diffuse large B-cell lymphoma** after three weeks of a firm, non-tender left supraclavicular node, fatigue, and 5 kg unintentional weight loss. **Past medical history:** type 2 diabetes on metformin, heart failure with reduced ejection fraction (LVEF 45%), and stage 3 CKD. Staging PET-CT shows **stage III disease**. LDH is elevated, ECOG is 1, giving an NCCN-IPI in the **high-intermediate range**. Because he has active disease, the accurate code is **C83.33** (DLBCL, intra-abdominal) or the appropriate site-specific code, **not C85.90**.

**MONITOR:** "Weight: 79 kg, down 5 kg over 3 weeks. **Functional status:** ECOG 1; G-8 = 12 → geriatric vulnerability flagged. **B symptoms:** unintentional weight loss >10% (present), night sweats (absent), fever (absent). Left supraclavicular node: 2.8 cm, firm, non-tender. **Baseline ECHO:** LVEF 45% → anthracycline limitation documented. **CrCl calculated:** stage 3 CKD → renally cleared agents **require dose adjustment**. Baseline CBC, CMP with LDH (elevated), albumin (low → OR 4.29 for grade 3+ toxicity). **Hepatitis B serology:** pending = must result **before** rituximab."

**EVALUATE:** "**Surgical pathology:** diffuse large B-cell lymphoma, GCB subtype by Hans algorithm, CD20+. Lugano stage III by PET-CT. **NCCN-IPI:** high-intermediate (age >60, LDH elevated, stage III, ECOG 1). **Geriatric assessment:** G-8 = 12 → unfit; **formal CGA completed;** HFrEF (**I50.22**), type 2 diabetes (**E11.65**), CKD stage 3 (**N18.3**), polypharmacy (8 medications). **Hepatitis B serology:** HBsAg, anti-HBc, anti-HBs ordered → **reactivation** with rituximab **can be fatal**."

**ASSESS:** "Active diffuse large B-cell lymphoma, intra-abdominal and nodal sites (**C83.33**; HCC 20). **Associated:** HFrEF LVEF 45% (**I50.22**) → precludes standard-dose doxorubicin; type 2 diabetes (**E11.65**) → **steroid-phase hyperglycemia anticipated**; CKD stage 3 (**N18.3**) → methotrexate contraindicated, monitor lenalidomide clearance; hypoalbuminemia (**E44.0**) → nutritional optimization before treatment. **Avoid C85.90**, subtype is confirmed. PHQ-2 screened: negative."

**TREAT:** "**Oncology-directed:** anthracycline-sparing regimen (R-CDOP, R-CEOP, or R-GCVP) under consideration given LVEF 45%; if patient ≥80 or very frail, **R-mini-CHOP** is the evidence-based **dose-reduced option**. Hepatitis B status must result **before** rituximab; antiviral prophylaxis arranged if anti-HBc positive. G-CSF prophylaxis given age ≥65. **PCP co-management:** intensify glucose monitoring during prednisone phases with sliding-scale insulin protocol; optimize heart failure management (continue guideline-directed medical therapy); monitor renal function per cycle. Nutrition support → **dietitian referral** for weight loss and hypoalbuminemia. **Early palliative care consultation placed** for symptom management. ACP documented (CPT 99497): surrogate named, code status discussed, goals of care aligned with high-intermediate prognosis. Return in 2 weeks or sooner for new symptoms."

## Clinical Documentation Elements

- **Document the confirmed histologic subtype:**<sup>1,4</sup> (e.g., DLBCL **C83.3x**, follicular **C82.xx** with grade, mantle cell **C83.1x**, MALT **C88.4x**, PTCL-NOS **C84.4x**) once hematopathology is available → subtype drives both code family and treatment; **never leave C85.90** as a permanent code when pathology specifies it
- **Document the anatomic site of involvement from imaging/pathology:**<sup>4</sup> Use 5th-character specificity (e.g., intra-abdominal **.3x**, intrathoracic **.2x**, multiple sites **.8x**) and disease status = active (**C8x.xx**) vs. in remission (suffix **'A'**)
- **Record stage under the Lugano classification and the applicable prognostic index:**<sup>1,13</sup> IPI for DLBCL/aggressive NHL, FLIPI for follicular lymphoma, MIPI for mantle cell lymphoma → score **informs prognosis and treatment intensity**
- **Re-confirm transformation status annually:**<sup>1,53</sup> A single growing node, rising LDH, or new B symptoms in known indolent disease **triggers re-biopsy** and a code update (e.g., follicular **C82.xx** → DLBCL **C83.3x**; CLL **C91.1x** → DLBCL **C83.3x** via Richter transformation)
- **Code each comorbidity at every applicable encounter:**<sup>46,62</sup> Cardiac function/LVEF (**I50.xx**) affects anthracycline eligibility, renal impairment (**N18.xx**) alters methotrexate/lenalidomide clearance, diabetes (**E11.xx**) requires steroid-phase glucose management,

cognition (**R41.xx/F03.xx**) and nutrition/albumin (**E44.xx, R63.4**) predict toxicity and guide intensity

- **Record the regimen, supportive prophylaxis, and monitoring plan:**<sup>1</sup> Document hepatitis B screening status and antiviral prophylaxis, G-CSF use, PJP prophylaxis (TMP-SMX), and distinguish curative-intent from disease-control intent
- **Document that active surveillance is an evidence-based decision**<sup>71</sup> when chosen for **low-burden indolent disease** (e.g., follicular lymphoma not meeting GELF criteria) → record scheduled monitoring intervals; this is a treatment strategy, **not the absence of care**
- **Document goals-of-care and advance-care-planning discussions**<sup>46</sup> (CPT 99497/99498), especially in patients ≥75 or with significant comorbidity → record surrogate, code status, and whether treatment intent is curative or palliative

## Reframing Common Documentation Shortcuts

| INSTEAD OF... <sup>1,4,11,53</sup>                           | DOCUMENT... <sup>1,16,46,53</sup>                                                                                                                                    |
|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 'Lymphoma' or 'NHL'                                          | 'Diffuse large B-cell lymphoma, intra-abdominal nodes, active ( <b>C83.33</b> ); stage III; NCCN-IPI high-intermediate'                                              |
| 'NHL, unspecified ( <b>C85.90</b> )' after pathology is back | Update to the confirmed subtype-and-site code once hematopathology resolves it; reserve <b>C85.90</b> for pending pathology only                                     |
| 'Small lymphocytic lymphoma, coded <b>C83.0x</b> '           | 'CLL/SLL ( <b>C91.10</b> ) — SLL and CLL are one biologic entity; nodal-predominant SLL is still <b>C91.1-</b> , not an NHL C-code'                                  |
| 'Known CLL, stable' despite a new growing node               | 'CLL with suspected Richter transformation → single enlarging node and rising LDH; <b>re-biopsy obtained</b> ; recode <b>C91.10</b> → <b>C83.3-</b> on confirmation' |
| 'On chemo'                                                   | ' <b>R-CHOP cycle 2 of 6</b> (rituximab-based); hepatitis B screened and negative; G-CSF prophylaxis; PJP prophylaxis with TMP-SMX'                                  |
| 'Follicular lymphoma, watch and wait'                        | 'Follicular lymphoma grade 1 ( <b>C82.01</b> ), low tumor burden by GELF, on <b>active surveillance with scheduled 3-month monitoring</b> '                          |
| 'Gastric lymphoma'                                           | 'Extranodal marginal zone ( <b>MALT</b> ) lymphoma of stomach ( <b>C88.4-</b> ); <i>H. pylori</i> positive, eradication therapy initiated'                           |
| 'Heart failure, continue meds' (NHL patient on doxorubicin)  | 'Heart failure, LVEF 45% ( <b>I50.-</b> ) → <b>anthracycline-sparing regimen selected</b> ; echocardiogram documented pre-treatment'                                 |



| INSTEAD OF... <sup>1,4,11,53</sup>                   | DOCUMENT... <sup>1,16,46,53</sup>                                                                                                                                  |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 'Diabetes, stable' during R-CHOP                     | 'Type 2 diabetes ( <b>E11.-</b> ) with steroid-related hyperglycemia during prednisone phases; <b>glucose monitoring intensified</b> and co-managed with oncology' |
| 'History of lymphoma (Z85.72)' while still monitored | Use the active C-code with MEAT while under surveillance; reserve <b>Z85.72</b> for <b>after treatment completion with no active monitoring</b>                    |

**ABBREVIATIONS:** NHL = non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; NCCN = National Comprehensive Cancer Network; IPI = International Prognostic Index; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; LDH = lactate dehydrogenase; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF = granulocyte colony-stimulating factor; PJP = Pneumocystis jirovecii pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole; GELF = Groupe d'Etude des Lymphomes Folliculaires; MALT = mucosa-associated lymphoid tissue; LVEF = left ventricular ejection fraction; MEAT = Monitor, Evaluate, Assess, Treat



### DOCUMENTATION REMINDER IS COMPREHENSIVE CODING

**Every NHL encounter** should document the **confirmed subtype**, anatomic site, and **status** (active vs. in remission), the **stage** and IPI/FLIPI score, the regimen with its prophylaxis and monitoring, and the **full comorbidity burden**: cardiac, renal, glycemic, cognitive, and nutritional.<sup>1,2,11,13</sup> Re-confirm transformation status **annually** so the code reflects the true disease course, and frame active surveillance as a deliberate, evidence-based plan.<sup>1,53</sup>

## 4 TREATMENT AND REFERRAL QUICK GUIDE

Treatment is subtype-dependent.<sup>1,2,11</sup> The two most common subtypes, **DLBCL (~40%)** and **follicular lymphoma (~20%)**, follow **opposite paradigms**: curative-intent chemoimmunotherapy versus active surveillance or disease control.<sup>1,11,21</sup> Treatment is initiated and directed by **hematology/oncology**; the **PCP role** is early recognition, urgent referral for excisional biopsy, pre-treatment screening (hepatitis B before rituximab, echocardiogram before anthracyclines), co-management of therapy-altered comorbidities, and reinforcing surveillance and adherence.<sup>1,53</sup> In older adults, functional status, **not chronological age**, drives treatment intensity; Comprehensive Geriatric Assessment guides whether a patient receives full-dose, dose-reduced, or supportive care.<sup>17,46,72</sup>

### Therapy Escalation Criteria

| TRIGGER <sup>1,2,12,53</sup>                                                                 | ACTION* <sup>1,34,53,73</sup>                                                                                                      |
|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>Persistent unexplained lymphadenopathy &gt;4 weeks or chronic refractory presentation</b> | <b>Excisional biopsy</b> with hematopathology review; refer to hematology/oncology → <b>do not rely on FNA</b> or empiric steroids |



| TRIGGER <sup>1,2,12,53</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | ACTION* <sup>1,34,53,73</sup>                                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Confirmed DLBCL, fit patient</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Oncology initiates curative-intent <b>R-CHOP x6</b> ; Pola-R-CHP is a Category 1 alternative <b>for IPI ≥2</b>                                       |
| <b>DLBCL in a patient ≥80 or very frail</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>R-mini-CHOP</b> (~50% dose reduction) = 2-year OS 59-66% in the <b>Peyrade/Oberic trials</b> ; prephase steroids ± vincristine for frail patients |
| <b>DLBCL with reduced LVEF or cardiac disease</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Anthracycline-sparing regimen (CDOP with liposomal doxorubicin, CEOP, or GCVP + rituximab); <b>echocardiogram/MUGA first</b>                         |
| <b>Relapsed/refractory DLBCL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>CAR T-cell therapy</b> (axi-cel, liso-cel, tisagenlecleucel) for eligible patients; bispecifics (epcoritamab, glofitamab) after ≥2 lines          |
| <b>Follicular lymphoma, low burden, asymptomatic</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>Active surveillance</b> : randomized trials show no OS benefit from early treatment; schedule <b>structured monitoring</b>                        |
| <b>Follicular lymphoma meeting GELF criteria (high burden)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>Chemoimmunotherapy</b> : bendamustine + rituximab or obinutuzumab, R-CHOP, R-CVP, or lenalidomide + rituximab (Category 2A)                       |
| <b>Mantle cell lymphoma</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>Fit</b> : intensive chemoimmunotherapy + autologous stem cell transplant; <b>elderly/frail</b> : BTK inhibitor + rituximab or BR                  |
| <b>CLL/SLL requiring treatment</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | BTK inhibitor (ibrutinib, acalabrutinib, zanubrutinib) or venetoclax + obinutuzumab = well tolerated orally in older adults                          |
| <b>Localized gastric MALT lymphoma</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>H. pylori eradication can induce remission</b> ; rituximab-based therapy or local radiation for non-gastric or refractory disease                 |
| <b>Suspected histologic/Richter transformation</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>Re-biopsy the discordant site</b> ; treat as DLBCL; update the code and escalate urgently to oncology                                             |
| <p><b>ABBREVIATIONS:</b> DLBCL = diffuse large B-cell lymphoma; FNA = fine-needle aspiration; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; Pola-R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone; IPI = International Prognostic Index; OS = overall survival; R-mini-CHOP = reduced-dose rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; LVEF = left ventricular ejection fraction; CDOP = cyclophosphamide, liposomal doxorubicin, vincristine, prednisone; CEOP = cyclophosphamide, etoposide, vincristine, prednisone; GCVP = gemcitabine, cyclophosphamide, vincristine, prednisone; MUGA = multigated acquisition scan; CAR = chimeric antigen receptor; axi-cel = axicabtagene ciloleucel; liso-cel = lisocabtagene maraleucel; GELF = Groupe d'Etude des Lymphomes Folliculaires; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; BTK = Bruton tyrosine kinase; BR = bendamustine + rituximab; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; MALT = mucosa-associated lymphoid tissue; ASCT = autologous stem cell transplant; FDA = U.S. Food and Drug Administration</p> <p><b>*Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions</b></p> |                                                                                                                                                      |

## NCCN-Aligned Treatment by Subtype, Fitness, and Patient Profile

| SUBTYPE/SETTING                            | GUIDELINE-ALIGNED APPROACH* <sup>1,34,40,53,73</sup>                                                                                           | KEY PCP NOTES* <sup>1,17,46,72</sup>                                                                                                                                         |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>DLBCL, fit (curative intent)</b>        | <b>R-CHOP x6</b> (category 1); Pola-R-CHP for IPI ≥2                                                                                           | <b>Aggressive but potentially curable</b> ; complete hepatitis B screening and echocardiogram <b>before</b> treatment                                                        |
| <b>DLBCL, age ≥80 or very frail</b>        | <b>R-mini-CHOP</b> (~50% dose reduction); prephase steroids ± vincristine                                                                      | 2-year OS 59–66%; G-CSF prophylaxis liberal at age ≥65; CARG/CRASH toxicity estimate <b>before</b> treatment                                                                 |
| <b>DLBCL, relapsed/refractory</b>          | <b>CAR-T</b> (axi-cel, liso-cel, tisagenlecleucel); <b>bispecifics</b> (epcoritamab, glofitamab); polatuzumab ± BR; tafasitamab + lenalidomide | CAR-T typically <b>requires ECOG 0–1</b> and a <b>specialized center</b> ; selinexor and loncastuximab in later lines                                                        |
| <b>Follicular, low burden asymptomatic</b> | <b>Active surveillance</b> (category 1)                                                                                                        | <b>Evidence-based</b> ; no OS benefit from early treatment; frame as active monitoring with scheduled visits, <b>not inaction</b>                                            |
| <b>Follicular, low burden symptomatic</b>  | <b>Single-agent rituximab</b> (375 mg/m <sup>2</sup> weekly x4)                                                                                | <b>Minimal toxicity</b> ; preferred in elderly when chemoimmunotherapy is not tolerable                                                                                      |
| <b>Follicular, high burden (GELF+)</b>     | <b>BR or obinutuzumab-based</b> ; R-CHOP; R-CVP; lenalidomide + rituximab                                                                      | Rituximab maintenance (every 8–12 weeks x2 years) <b>after chemoimmunotherapy</b> is category 1                                                                              |
| <b>Mantle cell lymphoma</b>                | <b>Fit</b> : intensive chemoimmunotherapy + ASCT; <b>frail</b> : BTK inhibitor + rituximab or BR                                               | Cyclin D1+/t(11; <sup>14</sup> ) <sup>+</sup> aggressive subtype; <b>not curable with standard therapy in most elderly</b> ; confirm with FISH                               |
| <b>CLL/SLL</b>                             | BTK inhibitor (acalabrutinib, zanubrutinib, ibrutinib) or venetoclax + obinutuzumab                                                            | Oral agents suit <b>frail elderly</b> ; monitor for <b>Richter transformation</b> (~5–10% of CLL); ibrutinib: monitor for <b>atrial fibrillation</b> and <b>hypertension</b> |
| <b>Extranodal MZL/MALT</b>                 | <b>H. pylori eradication</b> (gastric); rituximab-based or local radiation (non-gastric/limited)                                               | <b>Often highly responsive</b> ; document <i>H. pylori</i> status and remission; eradication can induce CR in ~ <b>75%</b> of localized gastric MALT                         |

| SUBTYPE/SETTING                       | GUIDELINE-ALIGNED APPROACH* <sup>1,34,40,53,73</sup>                      | KEY PCP NOTES* <sup>1,17,46,72</sup>                                                                         |
|---------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>PTCL-NOS and aggressive T-cell</b> | <b>Anthracycline-based chemotherapy</b> (CHOP/CHOEP); specialist-directed | Poorer prognosis than most B-cell NHL; confirm T-cell phenotype by IHC; clinical trial enrollment encouraged |

**ABBREVIATIONS:** DLBCL = diffuse large B-cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; Pola-R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone; IPI = International Prognostic Index; R-mini-CHOP = reduced-dose rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; OS = overall survival; G-CSF = granulocyte colony-stimulating factor; CARG = Cancer and Aging Research Group; CRASH = Chemotherapy Risk Assessment Scale for High-Age patients; CAR = chimeric antigen receptor; axi-cel = axicabtagene ciloleucel; liso-cel = lisocabtagene maraleucel; BR = bendamustine + rituximab; ECOG = Eastern Cooperative Oncology Group performance status; GELF = Groupe d'Etude des Lymphomes Folliculaires; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; ASCT = autologous stem cell transplant; BTK = Bruton tyrosine kinase; FISH = fluorescence in situ hybridization; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; MZL = marginal zone lymphoma; MALT = mucosa-associated lymphoid tissue; CR = complete remission; PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP = cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; NHL = non-Hodgkin lymphoma; IHC = immunohistochemistry; FDA = U.S. Food and Drug Administration

**\*Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**



### CLINICAL PEARL — SUBTYPE & FUNCTION > CHRONOLOGIC AGE

**Treat NHL by subtype and function, not chronological age.**<sup>1,46</sup> **R-CHOP** applies to **fit DLBCL patients, not to:** indolent subtypes, CLL/SLL, and or uniformly across very frail patients.<sup>1,3,53</sup> In the landmark **R-mini-CHOP trials**, patients aged  $\geq 80$  with DLBCL achieved 2-year OS of **59–66%** with dose-attenuated chemoimmunotherapy, establishing that **curative-intent treatment is feasible** in selected older adult patients.<sup>73</sup> The decision lever is **Comprehensive Geriatric Assessment** (ADL/IADL, cognition, nutrition, and comorbidity) which determines full-dose, dose-reduced (**R-mini-CHOP**), or supportive care, and reduces toxicity when used to guide care.<sup>17,46,72</sup>

## Non-Pharmacologic Care and Supportive Interventions

| INTERVENTION                              | TARGET/RECOMMENDATION                                                                            | NOTES                                                                                                                                  |
|-------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| <b>Nutritional optimization</b>           | Assess and correct <b>before treatment</b> ; <b>albumin</b> as a prognostic marker <sup>46</sup> | Hypoalbuminemia is the <b>strongest modifiable predictor</b> of grade 3+ toxicity ( <b>OR 4.29</b> ); dietitian referral <sup>74</sup> |
| <b>Low-intensity physical activity</b>    | Walking programs within tolerance during treatment <sup>75</sup>                                 | Safe; associated with <b>reduced fatigue and preserved function</b> <sup>76</sup>                                                      |
| <b>Comprehensive Geriatric Assessment</b> | <b>Before treatment</b> for older adults with tolerance concerns <sup>17,72</sup>                | ADL/IADL, Mini-Cog, nutrition, polypharmacy, social support; G-8, VES-13, CARG, CRASH tools <sup>46</sup>                              |

| INTERVENTION                                         | TARGET/RECOMMENDATION                                                                         | NOTES                                                                                                                    |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>Infection-prevention education</b>                | Hygiene, crowd avoidance, <b>prompt fever reporting</b> <sup>66</sup>                         | Prolonged B-cell depletion (6-12 months) <b>raises infection risk</b> ; PJP prophylaxis during therapy <sup>66</sup>     |
| <b>Caregiver engagement for oral targeted agents</b> | Pill organizers, written hold/reduce criteria, pharmacist support <sup>77</sup>               | Polypharmacy and cognitive impairment <b>complicate</b> ibrutinib/venetoclax/lenalidomide <b>adherence</b> <sup>78</sup> |
| <b>Active-surveillance education</b>                 | Explain that monitoring is evidence-based, <b>not inaction</b> ; schedule visits <sup>1</sup> | Reduces 'untreated' anxiety in low-burden indolent FL and maintains engagement <sup>71</sup>                             |
| <b>Goals-of-care and advance care planning</b>       | <b>At diagnosis</b> in frail/elderly; document directives and surrogate <sup>79,80</sup>      | Early palliative integration <b>improves quality of life</b> without shortening survival <sup>81</sup>                   |

**ABBREVIATIONS:** OR = odds ratio; ADL = activities of daily living; IADL = instrumental activities of daily living; G-8 = Geriatric 8 screening tool; VES-13 = Vulnerable Elders Survey-13; CARG = Cancer and Aging Research Group; CRASH = Chemotherapy Risk Assessment Scale for High-Age patients; PJP = Pneumocystis jirovecii pneumonia; FL = follicular lymphoma

## Medication Safety and Key Interactions

| DRUG/CLASS                                         | INTERACTION/TOXICITY*                                                                                                                              | CLINICAL ACTION*                                                                                                                                                                       |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Rituximab (anti-CD20)</b>                       | <b>HBV reactivation</b> = potentially fatal even in resolved infection (anti-HBc+/HBsAg-); PJP and prolonged B-cell depletion <sup>16</sup>        | <b>Mandatory</b> HBsAg/anti-HBc/anti-HBs <b>before start</b> ; antiviral prophylaxis (entecavir/tenofovir) when indicated; TMP-SMX for PJP <sup>66</sup>                               |
| <b>Venetoclax</b>                                  | <b>TLS within hours of first dose</b> → hyperkalemia and acute kidney injury <sup>53</sup>                                                         | <b>TLS risk stratification</b> ; ramp-up dosing; allopurinol, hydration, electrolyte monitoring; do not accelerate the schedule <sup>53</sup>                                          |
| <b>Ibrutinib + CYP3A4 inhibitors</b>               | Azole antifungals, clarithromycin, and grapefruit <b>raise ibrutinib exposure</b> up to 24-fold → increasing AF, bleeding, infection <sup>82</sup> | <b>Avoid strong CYP3A4 inhibitors</b> ; reduce dose or hold if unavoidable; <b>avoid grapefruit</b> <sup>82</sup>                                                                      |
| <b>Ibrutinib, bleeding and atrial fibrillation</b> | <b>Impaired platelet aggregation</b> ; new-onset AF in ~ <b>3%-16%</b> (off-target TEC kinase) <sup>82</sup>                                       | <b>Hold 3 days</b> (minor procedures) or <b>7 days</b> (major procedures) <b>around surgery</b> ; monitor BP and rhythm every visit; hematology input on anticoagulation <sup>82</sup> |

| DRUG/CLASS                                  | INTERACTION/TOXICITY*                                                                              | CLINICAL ACTION*                                                                                                                                       |
|---------------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Doxorubicin (in R-CHOP)</b>              | <b>Cumulative anthracycline cardiotoxicity</b> , amplified by CHF/CAD/LVEF <50% <sup>15</sup>      | Echocardiogram or MUGA <b>before treatment</b> ; substitute liposomal doxorubicin or anthracycline-free regimen in high-risk patients <sup>15,83</sup> |
| <b>Corticosteroids (prednisone in CHOP)</b> | <b>Hyperglycemia</b> during steroid phases; mood change; infection <sup>84</sup>                   | <b>Intensify glucose monitoring</b> (postprandial, not fasting alone); adjust hypoglycemics proactively; co-manage with oncology <sup>84</sup>         |
| <b>Lenalidomide</b>                         | Renal clearance → <b>accumulation causes</b> : cytopenias, neurotoxicity, VTE in CKD <sup>85</sup> | Calculate CrCl (Cockcroft-Gault) <b>before start</b> ; dose-adjust per renal function; VTE prophylaxis; monitor renal function <sup>85</sup>           |
| <b>Obinutuzumab (anti-CD20)</b>             | Rare <b>JC virus-related PML</b> ; infusion reactions <sup>86</sup>                                | Consider PML with new neurologic symptoms → prompt MRI and neurology referral <sup>1,66</sup>                                                          |

**ABBREVIATIONS:** HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; PJP = Pneumocystis jirovecii pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole; TLS = tumor lysis syndrome; CYP3A4 = cytochrome P450 3A4; AF = atrial fibrillation; BP = blood pressure; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; CHF = congestive heart failure; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; VTE = venous thromboembolism; CKD = chronic kidney disease; CrCl = creatinine clearance; JC = John Cunningham; PML = progressive multifocal leukoencephalopathy; MRI = magnetic resonance imaging; FDA = U.S. Food and Drug Administration

**\*Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

## When to Refer

| CRITERION                                                                | SPECIALIST* <sup>1,12,79</sup>    | URGENCY* <sup>87,88</sup> |
|--------------------------------------------------------------------------|-----------------------------------|---------------------------|
| <b>SVC syndrome, tumor lysis, cord compression, or airway compromise</b> | Emergency department              | <b>Emergent</b>           |
| <b>Febrile neutropenia during/after chemotherapy</b>                     | Emergency department/<br>oncology | <b>Emergent</b>           |
| <b>Rapidly enlarging adenopathy with B-symptoms</b>                      | Hematology/oncology               | Urgent (same/next day)    |
| <b>Suspected histologic or Richter transformation</b>                    | Hematology/oncology               | Urgent (same/next day)    |
| <b>New neurologic symptoms in a known NHL patient</b>                    | Hematology/oncology/<br>neurology | Urgent                    |

| CRITERION                                                              | SPECIALIST* <sup>1,12,79</sup>                    | URGENCY* <sup>87,88</sup> |
|------------------------------------------------------------------------|---------------------------------------------------|---------------------------|
| <b>Persistent unexplained lymphadenopathy &gt;4 weeks</b>              | Surgery (excisional biopsy) → hematology/oncology | Expedited (1–2 weeks)     |
| <b>Supraclavicular/epitrochlear node or node &gt;2 cm, hard, fixed</b> | Surgery → hematology/oncology                     | Expedited                 |
| <b>Confirmed NHL needing systemic therapy</b>                          | Hematology/oncology (first-line treatment)        | Routine-expedited         |
| <b>Persistent skin lesions unresponsive to dermatology</b>             | Dermatology → hematology/oncology                 | Routine                   |
| <b>Goals-of-care/symptom needs in advanced disease</b>                 | Palliative care                                   | Routine                   |

**ABBREVIATIONS:** NHL = non-Hodgkin lymphoma; SVC = superior vena cava

**\*Consult institutional protocols for specific referral pathways and timelines**

## Follow-Up Timing

| PHASE                                | PCP FOLLOW-UP FOCUS <sup>13,15</sup>                                                          | TIMING <sup>1,3</sup>                                                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>CBC with differential</b>         | <b>Before each chemotherapy cycle;</b> weekly in dose-dense regimens; each surveillance visit | ANC <500 → neutropenic precautions; <b>febrile neutropenia is an emergency;</b> platelets <50,000 → hold per protocol |
| <b>Comprehensive metabolic panel</b> | <b>Before each cycle;</b> more often during venetoclax ramp-up                                | Creatinine, electrolytes (TLS window), LFTs; >2–3x ULN <b>may require holding an agent</b>                            |
| <b>LDH</b>                           | Baseline, pre-treatment, each restaging PET-CT                                                | A rising LDH in known indolent lymphoma <b>raises transformation concern</b> → re-biopsy                              |
| <b>Hepatitis B serology/ HBV DNA</b> | <b>Serology ONCE before rituximab;</b> HBV DNA every 3–6 months on prophylaxis                | HBsAg+ or anti-HBc+ → antiviral prophylaxis <b>before and ≥12 months after</b> last rituximab dose                    |
| <b>Echocardiogram/ MUGA</b>          | <b>Once before anthracycline;</b> repeat if symptoms develop                                  | LVEF below institutional threshold → <b>cardio-oncology input;</b> anthracycline-free regimen                         |
| <b>PET-CT (Deauville)</b>            | <b>End of induction;</b> interim after ~2 cycles for selected high-risk                       | <b>Deauville 4–5</b> at end of induction = <b>treatment failure;</b> 1–3 = <b>complete response</b>                   |

| PHASE                                        | PCP FOLLOW-UP FOCUS <sup>13,15</sup>                                  | TIMING <sup>1,3</sup>                                                                                           |
|----------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| <b>Blood pressure and rhythm (ibrutinib)</b> | <b>Every visit</b> on ibrutinib                                       | New hypertension in ~ <b>20%-30%</b> and AF in ~ <b>6%-16%</b> ; prefer non-CYP3A4-inhibiting antihypertensives |
| <b>Geriatric/functional reassessment</b>     | <b>Each visit during treatment;</b> at least annually in surveillance | ADL/IADL decline, new cognitive impairment, or >5% weight loss → <b>reassess plan</b>                           |

**ABBREVIATIONS:** CBC = complete blood count; ANC = absolute neutrophil count; TLS = tumor lysis syndrome; LFT = liver function test; ULN = upper limit of normal; LDH = lactate dehydrogenase; PET-CT = positron emission tomography-computed tomography; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; MUGA = multigated acquisition scan; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; CYP3A4 = cytochrome P450 3A4; ADL = activities of daily living; IADL = instrumental activities of daily living

## Comorbidity Management — Primary Care Role

| COMORBIDITY                                  | APPROACH <sup>1,46,82,84</sup>                                                      | CAUTION* <sup>74,89</sup>                                                                |
|----------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| <b>Heart failure/cardiac disease (I50.-)</b> | Echocardiogram <b>before</b> anthracycline; favor CDOP/CEOP/GCVP in cardiac disease | Doxorubicin cardiotoxicity is <b>cumulative and amplified at LVEF &lt;50%</b>            |
| <b>Diabetes mellitus (E11.-)</b>             | <b>Intensify glucose monitoring</b> during prednisone phases; adjust agents         | <b>Steroid-driven hyperglycemia</b> can be severe; co-manage with oncology               |
| <b>Chronic kidney disease (N18.-)</b>        | Calculate CrCl <b>before</b> renally cleared agents; monitor function               | Affects methotrexate and lenalidomide clearance; <b>avoid nephrotoxins</b>               |
| <b>Hepatitis B (B18.-, Z22.51)</b>           | Screen and arrange antiviral prophylaxis <b>before</b> rituximab                    | <b>Reactivation can be fatal</b> , including in anti-HBc+/HBsAg– patients                |
| <b>Hypertension on ibrutinib (I10)</b>       | Monitor BP <b>every visit</b> ; calcium channel blocker preferred                   | <b>Avoid:</b> diltiazem/verapamil (CYP3A4 interaction with ibrutinib)                    |
| <b>Cognitive impairment (G31.84)</b>         | <b>Mini-Cog</b> ; caregiver involvement; written dosing schedules                   | <b>Raises:</b> medication-error, delirium, and consent risk during treatment             |
| <b>Malnutrition/frailty (E44.-, R54)</b>     | Nutritional optimization and functional assessment <b>before</b> treatment          | <b>Hypoalbuminemia</b> (OR 4.29) <b>and frailty</b> predict toxicity and hospitalization |



| COMORBIDITY                 | APPROACH <sup>1,46,82,84</sup>                               | CAUTION <sup>*74,89</sup>                                                                       |
|-----------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Polypharmacy (Z79.-)</b> | Medication review (Beers); <b>deprescribe</b> where possible | Drug-drug interactions with: ibrutinib, venetoclax, and lenalidomide → <b>compound toxicity</b> |

**ABBREVIATIONS:** LVEF = left ventricular ejection fraction; CrCl = creatinine clearance; HBsAg = hepatitis B surface antigen; BP = blood pressure; CYP3A4 = cytochrome P450 3A4; OR = odds ratio; FDA = U.S. Food and Drug Administration  
**\*Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

## Cost-Smart Options

| BRAND (EST. COST) <sup>90-92</sup>                                                                          | GENERIC/ALTERNATIVE (EST. COST) <sup>93-96</sup>                                        | EST. SAVINGS                                                                                         | COST-SMART TIP <sup>1,97,98</sup>                                                                                                |
|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Originator rituximab (Rituxan) (~\$3,800-\$4,000/mo Medicare Part B pay or cost pre-biosimilar)</b>      | Rituximab <b>biosimilars</b> (rituximab-pvvr, -arrx, -abbs) (~\$1,700/mo by 2023)       | ~\$33,000-\$46,000/yr in total medication costs; hospital acquisition price declined 63% (2020-2024) | <b>Biosimilars are interchangeable</b> for NHL; confirm formulary preference; 84% adoption by 2024                               |
| <b>Ibrutinib (Imbruvica) (~\$12,000/30-day supply)</b>                                                      | Acalabrutinib (Calquence) or zanubrutinib (Brukinsa) (~\$11,400-\$12,500/30-day supply) | ~\$47,000 per patient over treatment course (including AE management)                                | Second-generation BTKis have <b>lower AF</b> (9% vs. 16%) and <b>hypertension</b> (9% vs. 23%); <b>no generic BTKi available</b> |
| <b>Continuous BTKi monotherapy (~\$140,000-\$150,000/yr indefinitely)</b>                                   | Fixed-duration venetoclax + obinutuzumab (~12 months; ~\$94,000 total)                  | ~\$46,000-\$150,000+ over 3-5 years                                                                  | Time-limited regimen with <b>comparable PFS</b> ; eliminates indefinite drug exposure and long-term AE costs                     |
| <b>Low-burden indolent FL — early chemoimmunotherapy (~\$50,000-\$75,000 per course)</b>                    | Active surveillance = no drug cost (~\$200-\$400/visit for H&P + labs)                  | <b>Avoids ~\$50,000-\$75,000</b> in first-line costs; many patients defer treatment for years        | <b>NCCN category 1</b> ; no OS benefit from early treatment; 19% of watchful-waiting patients untreated at 10 years              |
| <b>Localized <i>H. pylori</i>-positive gastric MALT — systemic chemoimmunotherapy (~\$30,000-\$50,000+)</b> | <i>H. pylori</i> eradication therapy (~\$100-\$300 for antibiotics + PPI)               | <b>Avoids ~\$30,000-\$50,000+</b> in systemic therapy                                                | <b>NCCN first-line</b> ; 75% CR with eradication alone; t(11;18)+ unlikely to respond                                            |

| BRAND (EST. COST) <sup>90-92</sup>                                                      | GENERIC/ALTERNATIVE (EST. COST) <sup>93-96</sup>                                                                     | EST. SAVINGS                                                                                         | COST-SMART TIP <sup>1,97,98</sup>                                                                                                           |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Preventable febrile neutropenia hospitalization (~\$25,000-\$40,000 per episode)</b> | G-CSF prophylaxis with biosimilar filgrastim (~\$200-\$280/dose) or biosimilar pegfilgrastim (~\$1,500-\$2,500/dose) | <b>~\$20,000-\$35,000</b> per avoided hospitalization; biosimilar G-CSF ~30-50% less than originator | NCCN category 1 for >20% FN risk; liberal use in patients ≥65; <b>biosimilar substitution appropriate</b>                                   |
| <b>Self-administered Part D oral agents (pre-IRA OOP: ~\$10,000-\$14,000/yr)</b>        | Medicare Part D \$2,000 <b>annual OOP cap</b> + MPPP (\$167/mo)                                                      | <b>~\$8,000-\$12,000/yr</b> in OOP savings                                                           | Hematologic cancer patients see greatest OOP reduction ( <b>~\$10,846/beneficiary</b> ); enroll in MPPP to avoid front-loaded January costs |

**ABBREVIATIONS:** BTKi = Bruton tyrosine kinase inhibitor; AF = atrial fibrillation; PFS = progression-free survival; AE = adverse event; FL = follicular lymphoma; H&P = history and physical; OS = overall survival; MALT = mucosa-associated lymphoid tissue; PPI = proton pump inhibitor; CR = complete response; G-CSF = granulocyte colony-stimulating factor; FN = febrile neutropenia; IRA = Inflation Reduction Act; OOP = out-of-pocket; MPPP = Medicare Prescription Payment Plan; FDA = U.S. Food and Drug Administration

**\*Costs are approximate US estimates and vary by institution, payer, and region. Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

## Patient Education and Adherence

**Non-Hodgkin lymphoma patient education is distinguished by two features:** the heterogeneity of the disease — spanning **indolent subtypes** (follicular lymphoma, marginal zone lymphoma) where active surveillance may be appropriate, to **aggressive subtypes** (DLBCL, Burkitt lymphoma) requiring urgent chemoimmunotherapy — and the **subtype-dependent survivorship horizon**, during which late effects (secondary malignancies, cardiovascular disease, infections from prolonged B-cell depletion) may **exceed the original lymphoma** in clinical significance.<sup>2,11</sup> In older adults, the additional challenge is that treatment intensity is **fitness-stratified**, meaning patients must understand that geriatric assessment-guided dose adjustments are evidence-based optimization, **not under-treatment**.<sup>17,45,46</sup> **Education should emphasize:** which symptoms require **emergency evaluation** (SVC syndrome, febrile neutropenia, tumor lysis syndrome, cord compression), why excisional biopsy is preferred over FNA, the meaning of B symptoms and their role in staging, the **rationale for active surveillance in indolent disease**, and the subtype-specific surveillance schedule that the PCP co-manages after oncology discharge.<sup>1,11,13,56</sup>



## DOCUMENTATION REMINDER — PATIENT EDUCATION

**Document the following** education topics, the patient and caregiver(s) present, materials provided, and patient understanding (**teach-back method**):

- **Diagnosis in plain language:**<sup>2</sup> Patient understands histologic subtype (e.g., follicular vs. DLBCL vs. marginal zone), grade, stage, and whether disease is indolent or aggressive
- **Warning symptoms and when to call 911:**<sup>56,66</sup> Facial/upper extremity swelling or stridor (SVC syndrome), temperature  $\geq 38.3^{\circ}\text{C}$  with neutropenia, new back pain with neurologic deficit, and **tumor lysis signs** (muscle cramps, decreased urine output, especially during venetoclax ramp-up)
- **B symptoms and their significance:**<sup>11</sup> Fever  $>38^{\circ}\text{C}$ , **drenching night sweats**, weight loss  $>10\%$  in 6 months affect staging; in indolent NHL under surveillance, new B symptoms may signal transformation requiring re-biopsy
- **Active surveillance rationale (when applicable):**<sup>1</sup> For asymptomatic low-burden indolent NHL, **surveillance is NCCN category 1** → early treatment has not improved OS; document specific triggers for therapy initiation (symptoms, end-organ threat, cytopenias, bulk)
- **Treatment toxicity awareness:**<sup>1</sup> **R-CHOP:** cardiac symptoms, vincristine neuropathy; BTK inhibitors: AF, hypertension, bleeding; **venetoclax:** TLS during ramp-up; **all anti-CD20 regimens:** prolonged B-cell depletion, infection risk, hepatitis B prophylaxis
- **Transformation awareness** (indolent subtypes):<sup>1</sup> Report disproportionate nodal growth, new B symptoms, rising LDH, or new extranodal disease → prompts **urgent re-biopsy**
- **GA-guided dose adjustment** (when applicable):<sup>17,46</sup> Document counseling that GA-guided dose reductions are evidence-based care shown to **reduce toxicity without compromising survival**, not under-treatment
- **Survivorship monitoring:**<sup>1,11,13,15</sup> **Aggressive NHL:** H&P + labs every 3–6 months for 5 years then annually; CT no more than every 6 months for 2 years; routine surveillance PET/CT discouraged after CR. **Indolent NHL:** similar schedule with ongoing transformation monitoring. **All subtypes:** cardiovascular risk management after anthracycline, secondary malignancy screening, infection vigilance during B-cell depletion
- **Advance care planning:**<sup>79,80</sup> Surrogate, code status, goals of care; CPT 99497/99498 billable during AWW; prioritize in frail older adults
- **Caregiver assessment:**<sup>45,46</sup> Document caregiver understanding of TLS signs, FN protocol, transformation red flags, and oral agent adherence support; screen for caregiver burden; refer to social work if needed

## Quality Metrics Tie-In

**No NHL-specific HEDIS or MIPS measures are currently active in MY2026**, but NHL management intersects cross-cutting quality domains: depression screening, cardiovascular risk management, geriatric safety, care transitions, and advance care planning.<sup>1,11</sup> NHL patients face elevated depression risk (HR 2.09), cardiovascular morbidity (heart failure SIR 3.9 in DLBCL survivors), steroid-induced hyperglycemia (47% during R-CHOP), high readmission rates (hematologic malignancy HR 2.26 vs. solid tumors), and prevalent polypharmacy (69% of older DLBCL patients on ≥5 medications). These cross-cutting measures **anchor quality reporting for any PCP managing an NHL patient in a value-based program.**

| MEASURE                                                                | STANDARD                                                                                                                                                                                                                | APPLICABILITY TO NHL*                                                                                                                                                                                                                           |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>HEDIS CBP: Controlling High Blood Pressure</b>                      | <b>Denominator:</b> adults 18–85 with hypertension<br><b>Numerator:</b> BP <140/90 mmHg<br><b>Exclusions:</b> hospice, ESRD, inpatient palliative care                                                                  | <b>Heart failure SIR 3.9</b> in DLBCL survivors after anthracycline-based therapy; ibrutinib causes hypertension in <b>~20–30%</b> ; NCCN recommends CVD risk factor management for <b>all anthracycline-exposed survivors</b> <sup>15,99</sup> |
| <b>HEDIS COA: Care for Older Adults — Medication Review</b>            | <b>Denominator:</b> MA enrollees ≥66, continuously enrolled<br><b>Numerator:</b> 2 sub-measures documented annually:<br>(1) functional status assessment,<br>(2) medication review,<br><b>Exclusions:</b> hospice, ESRD | <b>69%</b> of older DLBCL patients have polypharmacy (≥5 medications; aHR 1.14 for mortality); ibrutinib has major CYP3A4 interactions with azole antifungals and clarithromycin; Beers Criteria review <b>at every visit</b> <sup>100</sup>    |
| <b>HEDIS COA: Care for Older Adults — Functional Status Assessment</b> | <b>Denominator:</b> enrollees ≥66<br><b>Numerator:</b> functional status assessment documented annually<br><b>Exclusions:</b> hospice, ESRD                                                                             | GA reveals deficits in <b>56%</b> of lymphoma patients despite preserved performance status; functional status drives regimen intensity (mini-CHOP vs. full CHOP) <sup>17,101</sup>                                                             |

| MEASURE                                                                                                | STANDARD                                                                                                                                                                                                                                                                                                                           | APPLICABILITY TO NHL*                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>HEDIS TRC: Transitions of Care — Patient Engagement After Inpatient Discharge</b>                   | <b>Denominator:</b> enrollees $\geq 18$ with inpatient discharge<br><b>Numerator:</b> 4 sub-measures within 30 days:<br>(1) notification of inpatient admission,<br>(2) receipt of discharge information,<br>(3) patient engagement after discharge,<br>(4) medication reconciliation post-discharge<br><b>Exclusions:</b> hospice | Hematologic malignancy is an independent readmission predictor (HR 2.26 vs. solid tumors); NHL in-hospital mortality 5.9%; polypharmacy (HR 1.78) and advanced stage (OR 2.85) are major drivers; PCP follow-up <b>within 7 days reduces readmission risk</b> <sup>102</sup>          |
| <b>HEDIS DMS-E: Utilization of the PHQ-9 to Monitor Depression Symptoms for Adolescents and Adults</b> | <b>Denominator:</b> enrollees $\geq 12$ with diagnosis of major depression or dysthymia AND elevated PHQ-9 $\geq 10$<br><b>Numerator:</b> follow-up PHQ-9 documented within 4–8 months of index elevated score<br><b>Exclusions:</b> hospice                                                                                       | Depression risk <b>2.09x higher</b> in NHL (HR 2.09); psychotropic drug use 16.4% vs. 5.1% in comparators; indolent NHL patients at persistently elevated risk ( <b>~30.7%</b> with clinically significant distress) <sup>103</sup>                                                   |
| <b>HEDIS ACP: Advance Care Planning</b>                                                                | <b>Denominator:</b> enrollees $\geq 66$<br><b>Numerator:</b> advance care plan or surrogate decision-maker documented, <b>OR</b> documentation that ACP was discussed but patient declined<br><b>Exclusions:</b> hospice                                                                                                           | GA-guided care <b>shapes regimen selection in older NHL</b> ; CPT 99497/99498 billable during AWW; particularly relevant for frail older adults where <b>fitness assessment drives treatment intensity</b> <sup>1,46</sup>                                                            |
| <b>HEDIS PCR: Plan All-Cause Readmission</b>                                                           | <b>Denominator:</b> enrollees $\geq 18$ with acute inpatient discharge<br><b>Numerator:</b> unplanned readmission within 30 days (lower is better)<br><b>Exclusions:</b> planned readmissions (maintenance chemotherapy, transplant), hospice, psychiatric                                                                         | Hematologic malignancy <b>HR 2.26 for readmission</b> ; polypharmacy (OR 1.78) and hypoalbuminemia are major drivers; G-CSF prophylaxis in patients $\geq 65$ prevents avoidable admissions; early palliative care <b>reduces non-beneficial emergency utilization</b> <sup>104</sup> |

| MEASURE                                       | STANDARD                                                                                                                                         | APPLICABILITY TO NHL*                                                                                                                                                                                                                  |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>HEDIS CDC: Comprehensive Diabetes Care</b> | <b>Denominator:</b> adults 18–75 with diabetes<br><b>Numerator:</b> HbA1c testing, eye exam, nephropathy screening<br><b>Exclusions:</b> hospice | <b>47%</b> develop hyperglycemia during <b>R-CHOP</b> ; B-NHL survivors have <b>4.41-fold increased DM risk</b> in first year post-diagnosis; do not defer HbA1c; intensify glucose monitoring during prednisone phases <sup>105</sup> |

**ABBREVIATIONS:** ESRD = end-stage renal disease; BP = blood pressure; SIR = standardized incidence ratio; DLBCL = diffuse large B-cell lymphoma; CVD = cardiovascular disease; MA = Medicare Advantage; aHR = adjusted hazard ratio; CYP3A4 = cytochrome P450 3A4; GA = geriatric assessment; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; HR = hazard ratio; NHL = non-Hodgkin lymphoma; PCP = primary care provider; PHQ-9 = Patient Health Questionnaire-9; ACP = advance care planning; CPT = Current Procedural Terminology; AWV = Annual Wellness Visit; G-CSF = granulocyte colony-stimulating factor; OR = odds ratio; HbA1c = hemoglobin A1c; B-NHL = B-cell non-Hodgkin lymphoma; DM = diabetes mellitus; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; HEDIS = Healthcare Effectiveness Data and Information Set; CMS = Centers for Medicare & Medicaid Services; MIPS = Merit-based Incentive Payment System; TLS = tumor lysis syndrome; FDA = U.S. Food and Drug Administration

**\*Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

## 5 CODING REMINDERS AND CASE EXAMPLES

### Coding Specificity

| ELEMENT                                  | DOCUMENTATION REQUIREMENT <sup>1,4,40,53</sup>                                                                                                                                         |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Subtype specificity</b>               | Document the confirmed histologic subtype with site (e.g., DLBCL <b>C83.3-</b> ; follicular <b>C82.-</b> ; mantle cell <b>C83.1-</b> ; MALT <b>C88.4-</b> ; PTCL-NOS <b>C84.4-</b> )   |
| <b>C85.90 is temporary only</b>          | Use NHL-unspecified <b>C85.90</b> only while pathology is pending; update on confirmation → permanent use is the most common NHL coding error                                          |
| <b>SLL is coded as CLL</b>               | Small lymphocytic lymphoma and CLL are one biologic entity → <b>C91.1-</b> (HCC 22), <b>never C83.0x</b> ; nodal-predominant SLL is still <b>C91.1-</b>                                |
| <b>Richter/histologic transformation</b> | On transformation to DLBCL, replace the code (CLL <b>C91.10</b> → DLBCL <b>C83.3-</b> , HCC 22 → HCC 20); this is a code replacement, <b>not an addition</b>                           |
| <b>Disease status &amp; remission</b>    | Use the <b>active C-code</b> with MEAT during treatment/surveillance; the 'A' suffix denotes documented remission; reserve <b>Z85.72</b> for <b>after treatment with no monitoring</b> |
| <b>Anatomic site (5th character)</b>     | <b>Specify</b> the involved nodal region or extranodal site rather than defaulting to 'unspecified site'                                                                               |

| ELEMENT                                          | DOCUMENTATION REQUIREMENT <sup>1,4,40,53</sup>                                                                                                                                                                              |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Grade for follicular lymphoma</b>             | Document grade I, II, IIIa, or IIIb; grade IIIb (FLBCL) <b>is treated as DLBCL</b>                                                                                                                                          |
| <b>Comorbidities co-managed during treatment</b> | Code heart failure ( <b>I50.-</b> ), diabetes ( <b>E11.-</b> ), CKD ( <b>N18.-</b> ), hepatitis B status ( <b>B18.-/Z22.51</b> ), malnutrition ( <b>E44.-</b> ), and long-term drug therapy ( <b>Z79.-</b> ) when addressed |
| <b>Annual re-documentation</b>                   | Active NHL ( <b>C82-C88</b> ) requires yearly MEAT evidence; a history code ( <b>Z85.72</b> ) eliminates mapping, NHL typically requires lifelong active monitoring                                                         |

**ABBREVIATIONS:** DLBCL = diffuse large B-cell lymphoma; MALT = mucosa-associated lymphoid tissue; PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified; NHL = non-Hodgkin lymphoma; SLL = small lymphocytic lymphoma; CLL = chronic lymphocytic leukemia; HCC = Hierarchical Condition Category; MEAT = Monitor, Evaluate, Assess, Treat; FLBCL = follicular large B-cell lymphoma; CKD = chronic kidney disease

## Annual Clinical Review and Confirmation

- **Annual review:**<sup>4</sup> An active NHL diagnosis remains current and must be **reassessed and documented with MEAT each year** → confirmed histologic subtype, anatomic site, Ann Arbor/Lugano stage, disease status, treatment phase, IPI/FLIPI score, and comorbidity burden
- **Visit modality:**<sup>4</sup> A face-to-face **or** synchronous audio-video telehealth encounter qualifies when it **supports meaningful clinical evaluation**; chart updates without an encounter do not satisfy MEAT
- **Histologic subtype verification:**<sup>1,53</sup> Before accepting **C85.90** (unspecified), **confirm subtype from pathology**: DLBCL → **C83.3-**; follicular → **C82.-**; mantle cell → **C83.1-**; MALT → **C88.4-**; PTCL-NOS → **C84.4-**; CLL/SLL → **C91.1-**; each follows a distinct treatment algorithm
- **Active disease vs. history:**<sup>4,13</sup> **Z85.72** (personal history) applies **only after** oncology has definitively closed surveillance; a patient on active treatment or post-treatment surveillance retains the active code (**C82-C88**); use the 'A' suffix only with oncologist-documented remission
- **Transformation check:**<sup>13,14</sup> Re-document transformation status **at each annual review** → any Richter or histologic transformation (single growing node, rising LDH, new B symptoms) triggers a **code replacement** (e.g., CLL **C91.10** → DLBCL **C83.3-**, HCC 22 → HCC 20), not an addition
- **Comorbidity carry-forward:**<sup>14,23</sup> Confirm that treatment-shaping comorbidities = cardiac (**I50.-**), diabetes (**E11.-**), renal (**N18.-**), hepatitis B status (**B18.-/Z22.51**), malnutrition (**E44.-**), and long-term drug therapy (**Z79.-**) remain on the problem list and are **independently coded each year** they are addressed



- **Avoid rollover:** Do not copy forward a prior note **without updating:** the histologic subtype and site, active-disease status, current stage, IPI/FLIPI, treatment phase and modifications, transformation status, and the comorbidity burden that documents regimen rationale

## Good Documentation - EHR Tips

- **EHR TIP — Smartphrase]** Build a **.nhl\_visit dot phrase** that **auto-populates:** subtype-specific code (**C83.3-** DLBCL, **C82.-** follicular with grade, **C83.1-** mantle cell, **C88.4-** MALT, **C84.4-** PTCL-NOS, **C91.1-** CLL/SLL), anatomic site (5th character), Ann Arbor/Lugano stage, disease status (active/remission/history), IPI/FLIPI score, and treatment-shaping comorbidities (I50.-, **E11.-**, **N18.-**, **B18.-/Z22.51**). Separate **.nhl\_survivor phrase** for **post-treatment:** subtype, last PET-CT date/Deauville score, LDH, and screening schedule. Eliminates unspecified C85.90 coding and supports MEAT in a single paste
- **[EHR TIP — Alert]** "Subtype Check" = flags **C85.90** when pathology-confirmed subtype exists elsewhere in chart. "Active vs. History Guard" = flags **Z85.72** while antineoplastic therapy remains on active medication list or surveillance imaging is ongoing. **"Transformation Prompt"** = at annual review, requires response to: "Any histologic/Richter transformation? Single growing node, rising LDH, new B symptoms?"
- **[EHR TIP — Best Practice]** Pin subtype-specific code with site and stage (e.g., "Diffuse large B-cell lymphoma, intra-abdominal nodes, **C83.33**, stage III, NCCN-IPI high-intermediate, active"), not "lymphoma." Code comorbidities individually (**I50.-**, **E11.-**, **N18.-**, **B18.-**). Reserve **Z85.72** only after oncology has definitively closed surveillance
- **[EHR TIP — Workflow]** **Fire BPA when: HBV serology absent before rituximab;** baseline echocardiogram/MUGA undocumented before anthracycline; CrCl unchecked before renally cleared agents; follicular lymphoma grade undocumented; **C85.90 persisting >30 days** for subtype upgrade; no MEAT encounter in 6 months. Flag transformation status undocumented at annual review
- **[EHR TIP — Order Set]** **"NHL Active Treatment":** CBC, CMP, LDH, uric acid, hepatitis B serology (HBsAg, anti-HBc, anti-HBs), echocardiogram/MUGA (if anthracycline planned), CrCl, PET-CT per protocol, pathology review. **"NHL Survivorship":** annual CBC, CMP, LDH, PET-CT/Deauville per schedule, HBV monitoring (if on prophylaxis), cardiac assessment (if prior anthracycline), nutrition screen

## Brief Case Examples

### SUCCESS: THREE-AXIS CODING, COMORBIDITIES LINKED, COORDINATED CARE

#### SCENARIO

A 74-year-old male with three weeks of a firm, non-tender left supraclavicular node, fatigue, and >10% weight loss. **PMH:** type 2 diabetes, heart failure (LVEF 45%), stage 3 CKD. Provider obtained

excisional biopsy with hematopathology review, confirmed diagnosis, and **documented the full clinical picture** through staging and treatment initiation:

**Documentation:** "C83.33: Active diffuse large B-cell lymphoma, intra-abdominal nodes, stage III, NCCN-IPI high-intermediate (pathology confirmed [date]). **Excisional biopsy** with hematopathology review; FNA avoided. Hepatitis B screened **before rituximab** → prophylaxis arranged. **I50.-**: Heart failure, LVEF 45% → anthracycline-sparing regimen selected. **E11.-**: Type 2 diabetes → glucose co-managed during steroid phases. **N18.-**: Stage 3 CKD → renal dosing confirmed. G-CSF prophylaxis initiated. Goals of care documented. Care coordinated with hematology-oncology, cardiology, endocrinology, and nephrology. Return [interval] or sooner for new symptoms."

**Outcome:** C83.33 (HCC 20) + I50.- + E11.- + N18.- mapped with full diagnostic and treatment course documented. **Every MEAT element present:** subtype-specific diagnosis with pathology confirmation, anatomic site, staging with prognostic index, treatment-shaping comorbidities coded independently and linked to regimen rationale (anthracycline-sparing for HF, glucose management for steroids, renal dosing for CKD), HBV prophylaxis preventing reactivation, G-CSF prophylaxis preventing avoidable admission, goals of care, multidisciplinary care coordination, and follow-up interval with return criteria. Diagnosis made by **excisional biopsy rather than FNA**. Subtype confirmed and coded specifically (HCC 20) rather than left on **C85.90** (HCC 21).

## PITFALL: UNSPECIFIED CODING AND OMITTED COMPLEXITY

### SCENARIO

A 74-year-old with an enlarging cervical node. Empiric prednisone had been given before biopsy. Presents for routine follow-up. PMH includes type 2 diabetes, heart failure, and stage 3 CKD.

**Documentation as written:** "74-year-old with lymphoma, stable. Continue care. Non-Hodgkin lymphoma, unspecified (C85.90)."

**Consequence:** (1) Subtype never specified: **C85.90** used **despite confirmed DLBCL** on pathology = most common NHL coding error. (2) Anatomic site defaulted to unspecified despite imaging documenting supraclavicular involvement. (3) Empiric steroids masked histology and risked a false-negative biopsy. (4) Hepatitis B **not screened before rituximab**. (5) Heart failure, diabetes, and CKD went uncoded, understating true complexity and the rationale for regimen modification. (6) No staging, IPI, treatment details, or goals of care documented. No MEAT elements present beyond a bare, inaccurate diagnosis label.

**RAF Impact:** C85.90 maps to HCC 21 (CNA RAF 0.671), whereas confirmed DLBCL (C83.3-) maps to HCC 20 (CNA RAF 1.136).<sup>9,10</sup> Beyond the RAF, the unspecified note **misrepresents** an aggressive, curable disease as undifferentiated, weakens authorization for subtype-directed therapy, and **fragments care coordination**.

**Fix:** Obtain excisional biopsy without empiric steroids; on pathology, update to the specific subtype/site code. **Corrected documentation:** "C83.33: Active diffuse large B-cell lymphoma, intra-abdominal nodes, stage III, NCCN-IPI high-intermediate. Hepatitis B screened → prophylaxis initiated. **I50.-**: Heart failure, LVEF 45% → anthracycline-sparing regimen. **E11.-**: Type 2 diabetes → steroid-phase glucose co-management. **N18.-**: Stage 3 CKD → renal dosing confirmed. Goals of care documented. Return [interval] or sooner for new symptoms." **Coding after fix:** C83.33 (HCC 20) + I50.- + E11.- + N18.- replaces **C85.90** = subtype-accurate, site-specific, active-disease coding with full clinical picture preserved.

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