Application of the Lugano Classification for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The PRoLoG Consensus Initiative (Part 1—Clinical)

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Our objective was to provide consensus recommendations from a consortium of academic and industry experts in the field of lymphoma and imaging for consistent application of the Lugano classification. **Methods:** Consensus was obtained through a series of meetings from July 2019 until September 2021 sponsored by the Pharma Imaging Network for Therapeutics and Diagnostics (PINTaD) as part of the PINTaD Response Criteria in Lymphoma Working Group (PRoLoG) consensus initiative. **Results:** Consensus recommendations clarified technical considerations for PET/CT and diagnostic CT from the Lugano classification, including updating the FDG avidity of different lymphoma entities, clarifying the response nomenclature, and refining lesion classification and scoring, especially with regard to scores 4 and 5 and the X category of the 5-point scale. Combination of metabolic and anatomic responses is clarified, as well as response assessment in cases of discordant or missing evaluations. Use of clinical data in the classification, especially the requirement for bone marrow assessment, is further updated on the basis of lymphoma entities. Clarification is provided with regard to spleen and liver measurements and evaluation, as well as nodal response. **Conclusion:** Consensus recommendations are made to comprehensively address areas of inconsistency and ambiguity in the classification encountered during response evaluation by end users, and such guidance should be used as a companion to the 2014 Lugano classification.

Key Words: Lugano classification; clinical recommendations; consensus; standardization

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In 2014, the Lugano classification (*1*) and its companion report (*2*) (together referred to here as Lugano 2014) provided a standardized approach to classifying response based on ^{18}F-FDG PET/CT. In particular, Lugano 2014 emphasized the importance of a 5-point scale (5-PS) for FDG-avid lymphomas along with a well-defined characterization of splenomegaly while maintaining many of the anatomic elements of the revised response criteria for malignant lymphoma, published in 2007 (*3*).

The Lugano classification has been widely adopted by academia, by the pharmaceutical industry, and in clinical practice for evaluation of Hodgkin lymphoma and non-Hodgkin lymphoma, leading to acceptance by regulatory agencies for drug approval and by treating physicians alike. Currently, hundreds of actively recruiting and ongoing investigational trials use the Lugano classification (https://clinicaltrials.gov).

As with any criteria, the application of the Lugano classification has uncovered some challenges in implementation resulting in nonuniform use, variable interpretation, and customized modifications with the potential to undermine effective comparisons between patient groups, treatment regimens, and outcome analyses. To address these challenges, volunteer leaders from industry and academia, including original authors of the Lugano classification, referred to as the PINTaD Response Criteria in Lymphoma Working Group (PRoLoG),

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sponsored by the Pharma Imaging Network for Therapeutics and Diagnostics (PINTaD; https://www.pintad.net), engaged in discussions from July 2019 until September 2021 to provide expert guidance on the consistent application of the Lugano classification.

This article is not intended to replace the classification but is proposed as a companion to Lugano 2014. Although other lymphoma response criteria have since been published (e.g., LYRIC 2016 (*4*) for immunomodulatory therapies and RECIL 2017 (*5*)), most of the current recommendations may also apply to the newer criteria as well.

The recommendations in this document focus on imaging aspects rather than implementation in clinical practice for treatment decisions. The recommendations hopefully will facilitate consistent imaging interpretation and response assessment during clinical trials and may be a valuable addition for health-care providers.

MATERIALS AND METHODS

Task forces (TFs) were created to evaluate technical and clinical considerations and descriptive ambiguities within the Lugano classification. A steering committee was formed to oversee the activities of each TF and to summarize, reconcile, and consolidate the recommendations from the regularly scheduled TF meetings. The TF members included independent research leaders and representatives from academic and scientific organizations ($n = 3$), industry ($n = 9$), clinical research organizations ($n = 13$), and other clinical trial specialists ($n = 4$). All meetings were held virtually, from July 2019 to September 2021.

TF meetings were recorded, and the minutes were transcribed and approved by TF members. Recommendations were based on a hierarchic approach, with evidence-based decisions providing the strongest level of support, followed by best practices and then expert consensus opinions. When evidence-based data or consensus was lacking, a call for future research on that topic was suggested. Additional recommendations from the TFs, primarily for advanced imaging technical considerations, will be available in a companion article (*6*).

The end user is any individual involved in the implementation of the Lugano classification—for example, clinical trialists, physicians, scientists, data managers, statisticians, scientific and medical writers, health-care providers, program coders, and regulatory personnel. The term *reviewer* in this document is defined as any physician responsible for assessing response in lymphoma, such as an imaging specialist (radiologist or nuclear medicine physician) or a clinical specialist (oncologist, hematologist, radiation oncologist).

IMAGING ACQUISITION CONSIDERATIONS

The use and frequency of PET/CT or diagnostic CT with contrast enhancement depend on several factors. These include the clinical question, lymphoma histology and stage, FDG avidity, and efficacy endpoints. In FDG-avid lymphomas, a diagnostic CT scan may not be required at each scheduled tumor assessment when ^{18}F-FDG PET/CT is scheduled; for example, when a clinical trial protocol specifies that ^{18}F-FDG PET/CT is required for each imaging visit, then no additional diagnostic CT examination may be needed. Similarly, an ^{18}F-FDG PET/CT scan may not be required at each time point; for example, ^{18}F-FDG PET/CT is usually discouraged for surveillance (*7,8*). Although the role of surveillance imaging is not established in clinical practice (*9–12*), diagnostic CT may still be required in follow-up of clinical trials using time-dependent endpoints (e.g., progression-free survival (*1*)).

In the Lugano classification, the term *PET/CT-based* refers to PET corrected for attenuation by CT, that is, for metabolic assessment and localization of lesions, whereas the term *CT-based* refers to diagnostic-quality CT for morphologic assessment.

FDG AVIDITY OF LYMPHOMA ENTITIES

Although most lymphomas are FDG-avid, metabolic imaging may be less reliable for response assessment in some histologies because of greater inter- or intraindividual lesion variability in ^{18}F-FDG uptake.

There are 3 lymphoma categories. The first category is routinely FDG-avid lymphoma (*2,13*) (e.g., Hodgkin lymphoma, diffuse large B-cell lymphomas, follicular lymphoma (*14–17*), mantle cell lymphoma (*18–20*), nodal peripheral T-cell lymphoma (*21–23*), lymphoblastic lymphoma (*24–26*), and Burkitt lymphoma (*27,28*)); these should be assessed by ^{18}F-FDG PET/CT and, when anatomic assessment is required, by diagnostic CT.

The second category is lymphoma that is generally not FDG-avid (e.g., small lymphocytic lymphoma and chronic lymphocytic leukemia); this category should be assessed with diagnostic CT and not with ^{18}F-FDG PET/CT, unless for suspected or documented transformation.

The third category is lymphoma that, although commonly FDG-avid, had variability in ^{18}F-FDG uptake, either interpatient or interlesional (e.g., some marginal-zone lymphomas (*29–31*) and some T-cell lymphomas (*32*), notably cutaneous T-cell lymphomas). There is no formal recommendation on which type of imaging is to be performed; it should be based on the lymphoma entity and can be aligned with health authorities. In general, baseline imaging may include ^{18}F-FDG PET/CT and diagnostic CT. Patients without FDG-avid lesions at baseline should be followed with diagnostic CT (unless transformation is suspected). In patients with FDG-avid lesions at baseline, PET/CT may be used for response assessment and rules for combination of metabolic and anatomic response should be prespecified in the protocol.

LESION CLASSIFICATION, SCORING, AND RESPONSE NOMENCLATURE

Common Lesion Classification and Response Nomenclature

CT. On CT, tumor lesions should be referred to as either target lesions (assessed quantitatively) or nontarget lesions (assessed qualitatively). Nodal and extranodal lesions should ideally be documented as separate classifications since they have different assessment rules.

^{18}F-FDG PET/CT. On ^{18}F-FDG PET, assessment nomenclature is designated as the 5-point scale (5-PS). The 5-PS is based on the single most metabolically active lesion (with visual or semiquantitative assessment), which can vary at each time point. SUVs that are captured (e.g., the most hypermetabolic lesion, reference regions) usually represent the SUV_{max}, in alignment with the Lugano classification. Other types of measurements (e.g., SUV_{peak} and SUV_{mean}) are being explored for use in clinical trials (*33,34*), and further work is required in this field to identify the optimal measure. Besides, metabolic assessments (e.g., metabolic tumor volumes) or radiomics may become more important in the future.

Both CT and PET/CT responses should be reported when available, and designated "M" for metabolic or "A" for anatomic, as well as the overall response (i.e., the response to be used for determining endpoints, integrating imaging response [metabolic, anatomic, or a combination of both, when available] and clinical data

when available) (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Scoring of Lesions on CT and ^{18}F-FDG PET/CT and Metabolic Response Category

Target lesions selected on CT at baseline should be FDG-avid, with higher uptake than in normal liver, for FDG-avid lymphoma. This means a 5-PS of greater than 3, although the 5-PS was not originally intended to be applied at baseline.

Protocol inclusion criteria for FDG-avid lymphoma should state that eligible subjects must have at least 1 FDG-avid lesion; the recommendation is that there be at least 1 lesion with higher intensity than in normal liver (for FDG-avid lymphomas) and at least 1 CT-measurable lesion (when anatomic measurements are required).

A score of 4 should be applied to lesion uptake greater than uptake in a large region of normal liver, that is, not to lesion uptake only moderately greater than in the liver as was originally stated in the Lugano classification. When a semiquantitative approach is used, this score applies to uptake greater than the SUV_{max} in a large region of normal liver.

A score of 5 should be applied to lesion uptake markedly greater than in the liver, to hypermetabolic new lesions, or to both, and the reason for assessing a score of 5 should be recorded (uptake or hypermetabolic new lesions or both). When a semiquantitative approach is used, this score applies to uptake at least 2 times the SUV_{max} in the liver since thresholds of both 2 times and 3 times have been used in published reports (*2,33,35–40*) and there is no further evidence to recommend one or the other. If such a semiquantitative approach is used, the threshold that will be applied should be defined a priori in the clinical study documents and reported (*41*).

The optimal threshold for response likely depends on the lymphoma entity, treatment, and timing; further research is recommended to define score 4 and score 5 (*35,39,40,42*).

When the metabolic response category is being evaluated, the overall metabolic uptake (i.e., intensity and extent) has to be considered along with the 5-PS. A visual score of 4 or 5 with reduced intensity and no increase in the extent is considered a partial metabolic response (PMR), whereas increased intensity or increased extent is considered progressive metabolic disease. Uptake of stable intensity with no increase in extent is considered no metabolic response (NMR).

The X category defined in the Lugano classification as areas of uptake unlikely to be related to lymphoma should not be considered a category by itself, and the reviewer should always assign a 5-PS in addition to X.

RESPONSE ASSESSMENT

Imaging Response Assessment

When the Lugano classification is used for FDG-avid lymphomas, the metabolic response assessed on ^{18}F-FDG PET/CT should take precedence over the anatomic response assessed on diagnostic CT. Although the definition of a PMR lacks an objective quantitative cutoff in the Lugano classification, there is insufficient evidence to further define a PMR for most lymphomas, and efforts at further standardization are warranted (e.g., delta SUV, change in metabolic tumor volume). Below are the rules for combining metabolic and anatomic responses in FDG-avid lymphomas when both modalities are available.

Acceptable Assessments of Imaging Complete Response (CR). For CR, acceptable assessments are, first, PET complete metabolic response (CMR) plus CT response (either complete anatomic response [CAR] or partial anatomic response) or stable anatomic disease and, second, PET CMR plus CT progressive anatomic disease within the same visit window—that is, the progressive disease seen on CT does not correlate with any metabolic progression.

Acceptable Assessments of Imaging Partial Response (PR). For PR, acceptable assessments are, first, PET PMR plus CT response (either CAR or partial anatomic response) or stable anatomic disease and, second, PET PMR plus CT progressive anatomic disease within the same imaging window—that is, the progressive disease seen on CT does not correlate with any metabolic progression.

Acceptable Assessments of Imaging Stable Disease. For stable disease, acceptable assessments are, first, PET NMR plus CT response (either CAR or partial anatomic response) or stable anatomic disease and, second, PET NMR plus CT progressive anatomic disease by a new anatomic lesion within the same imaging window—that is, the new lesion seen on CT is not showing hypermetabolism suggestive of lymphoma.

The TFs recognize (but do not recommend, since metabolic response should take precedence over anatomic response) the practice by which imaging response based on PET/CT (e.g., CMR/PMR) is downgraded when CT shows progressive anatomic disease. Such cases may be reassigned as overall CR/PR on the basis of clinical review (i.e., the hematology–oncology review that is performed in some clinical trials after the imaging review), biopsy, or follow-up imaging.

In the Lugano classification (*1*), CMR, PMR, and NMR require the absence of new lesions for FDG-avid lymphomas. For clarification, any new lesion not considered to be lymphoma, whether metabolically active or not, does not represent disease progression.

Further Considerations for Discordant Cases Between Diagnostic CT and ^{18}F-FDG PET/CT

In routinely FDG-avid lymphomas for which the ^{18}F-FDG PET results are discordant with diagnostic CT, the PET results should supersede the CT interpretation with the caveat that the overall time point response can be overridden during a clinical review by integration of clinical data into the imaging assessment, if applicable, or if additional data such as biopsy or imaging follow-up are subsequently provided. For example, when the ^{18}F-FDG PET is CMR (or PMR or NMR) but CT demonstrates new or growing metabolically inactive lesions, it is unlikely that this finding represents lymphoma in a routinely FDG-avid histology, and CR (or PR or stable disease, respectively) can usually be assigned.

Biopsy of a growing or new lesion, or else follow-up, should be strongly encouraged, as clinically appropriate, as well as a search for alternative causes. Positive results on biopsy (including via endoscopy if a gastrointestinal lesion) or cytology (if effusion), or follow-up confirmation of disease, would preclude an overall time point response of CR (or PR or stable disease, respectively) and be considered progressive disease. Progressive disease would then need to be backdated to the first appearance of the growing or new lesion. This should be prespecified in the study documents.

In lymphomas that are not FDG-avid, CT results should supersede PET for the imaging time point response assessments, and the CT-based response as per the Lugano classification (*1*) should be used. If CT scan visits are missing, the imaging time point response would not be evaluable unless PET/CT has been performed and the CT portion of the PET/CT is of diagnostic quality, based on reviewer judgment, to permit accurate tumor burden assessments.

The "FDG Avidity of Lymphoma Entities" section provides recommendations for lymphomas with variability in ^{18}F-FDG uptake.

Assessment of Response When PET/CT or Diagnostic CT Imaging Visits Are Missing or Not Done as Per Protocol

Best-practice recommendations for PET scheduling in pivotal clinical trials, when acceptable and reasonable, are to time the frequency of PET/CT acquisitions with the anticipated response to the intervention and provide details for superseding rules (i.e., how to carry over responses when one or the other modality is not done at every visit).

When PET/CT is not available but diagnostic CT is, the PET/CT response can be carried forward from the prior visit to provide an imaging response assessment as long as the diagnostic CT scan does not suggest disease deterioration (or clinical status, with regard to overall response, in cases in which clinical review is performed).

When diagnostic CT is not available but there has been no substantial change on ^{18}F-FDG PET/CT, the results of the prior CT scan can be carried forward. On occasion, the CT portion of PET/CT can be used to assess the CT disease burden if considered of suitable diagnostic quality.

It is common for clinical trials to use a modified Lugano classification (i.e., with variations from the original publication). In such a case, there should be a requirement that *modified* be defined.

INCORPORATION OF CLINICAL DATA

Imaging and Clinical Response Assessments

Best-practice opinions suggest that a paradigm of independent review by imaging specialists followed by clinical oncology review to update results according to clinical and laboratory data introduces the least bias into the process while providing the most reliable and consistent results. For studies not using an independent clinical oncology review, it is suggested that imaging reviewers receive some limited clinical information, to be prospectively defined in the protocol.

Clinical Data Requirements

There is no requirement for integrating clinical information per Lugano guidance, except for bone marrow (BM) biopsy (BMB) and aspiration for lymphoma histologies when PET/CT may not be a substitute for this information.

The clinical data that should be provided to the reviewer must be defined in the study documents and be consistently recorded and provided as a structured report or dossier with pertinent clinical information (e.g., BMB results, lesion biopsy/fluid evaluation if performed, concomitant therapy that could affect scan results such as the use of colony-stimulating factor, infection/inflammation or other information that can confound PET/CT and diagnostic CT findings, and clinical and laboratory information).

In general, physical examination data should not be provided to the central reviewer since imaging should take precedence over clinical examination for lesion measurement, except for lesions that would not be captured on imaging (e.g., scalp and lower extremities). As well, when feasible, appropriate but limited clinical history and information should be provided to imaging reviewers to better select lesions at baseline (e.g., prior radiation therapy).

Recommendations for Assessment of BM Involvement

Although BM samples should usually be obtained before the start of therapy, many patients with relapsed or refractory disease have BMB results in the prebaseline period that could eliminate the need for a repeat BMB before receiving therapy, especially when the prebaseline BMB results were positive. In general, one should consider whether BM results from the prebaseline period may be used for the baseline, within a time frame to be prespecified per the protocol (typically BM results should be dated no longer than 3 mo before the start of therapy and unless clinical changes suggest otherwise).

The requirement for repeat BMB in a clinical trial is based on the setting (e.g., lymphoma entity, FDG avidity, study phase, and endpoints) and should be prespecified in the study documents.

BM involvement in diffuse large B-cell lymphoma and Hodgkin lymphoma tends to be focal, whereas diffuse avidity suggests an inflammatory process. Rarely, predominantly BM-based disease in diffuse large B-cell lymphoma can present with intense, diffuse uptake. Involvement by follicular and other low-grade lymphomas may not be apparent because of the indolent nature of the diseases (*43*).

FDG-Avid Lymphomas. When the results of BMB are negative at baseline, it is reasonable to assign a CR as the overall response without repeating the BMB if the patient achieves a metabolic CMR.

In Hodgkin lymphoma and diffuse large B-cell lymphoma, a baseline BMB may not be required in all patients because PET/CT may substitute for BM evaluation as per the Lugano classification (*1,41,44–47*). When the patient achieves a CMR, it is reasonable to assign a CR as the overall response, whatever the status of BM sampling at baseline. The requirement for BMB should be prespecified in the clinical study protocol.

In follicular lymphoma, although there is new evidence that BM sampling may not be mandatory in all trials (*48–50*), PET/CT does not uniformly substitute for BMB for staging and response assessment and may still need to be obtained, especially in patients without BM uptake on ^{18}F-FDG PET/CT at baseline. It should be prespecified in study documents whether a patient who had positive BM uptake on PET at baseline and achieves a PET/CT CMR can be assigned a CR as the overall response if BM sampling is not done.

In FDG-avid lymphomas for which a BMB during or at the end of treatment shows lymphoma involvement, the best response cannot be better than PR, even with an otherwise CMR.

Lymphomas That Are Not FDG-Avid or Have Variable ^{18}F-FDG uptake. When BM sampling is negative at baseline, it is reasonable to assign a CR as overall response if the patient achieves a CAR (and CMR if PET/CT is available). When BM sampling is positive or the result is unknown at baseline, and BM sampling is not obtained or is positive during or at end of treatment, but the patient achieves a CAR (and CMR if PET/CT is available), it should be downgraded to a PR as overall response.

Situations in Which BMB findings Are Indeterminate. When BMB findings are indeterminate, it is reasonable to downgrade a PET CMR to PR for lymphomas where PET cannot substitute to BMB.

EVALUATION OF SPLEEN, LIVER, AND NODAL INVOLVEMENT

Spleen and Liver Size and Nodules

Spleen. The expert judgment of the reviewer should be used when the size measurement is inconsistent with the rest of the tumor burden. Spleen size can vary with factors unrelated to lymphoma involvement, including patient age, body dimensions, and sex (*51*); nonmalignant conditions (e.g., enlargement from portal hypertension or splenic vein thrombosis); technical factors such as

respiratory motion on CT; and prior injury or trauma. Thus, the expert reviewer should determine the status of the spleen with respect to splenomegaly when measurements are close to the 13-cm threshold before, during, or after treatment.

Liver. In alignment with the Lugano classification, liver size should no longer be considered part of the assessment. Nodules or masses in the spleen and liver should be recorded as part of the anatomic tumor lesion assessment (target lesion/nontarget lesions). When standard diagnostic CT is acquired, intravenous injection of a contrast agent during anatomic imaging, unless contraindicated, is paramount for the evaluation of lesions in solid organs, which may not be visible without a contrast agent.

Modality for Spleen Measurement

The TFs recommend that when splenic size assessments are required, diagnostic CT should be used and vertical length be reported (Supplemental Fig. 1). If diagnostic CT is not available, the splenic measurement from the CT portion of PET may be used if considered to be of acceptable quality by the reviewer; if the CT portion of PET is considered of unacceptable quality for measurement (e.g., major breathing motion artifacts), splenic measurements on PET should be discouraged and, unless splenic size would not have an impact on the outcome, should be reported as not evaluable.

Clinical palpation is not considered adequate for determination of splenic length.

New and Recurrent Splenomegaly

As defined in the Lugano classification, an increase of at least 2.0 cm should be applied to both new and recurrent splenomegaly. Progression should be assessed compared with the nadir (which can be the baseline).

Liver Used as a Reference for the 5-PS

When the liver is used as a reference site, the reference region in the liver should avoid the liver margins and any focal hepatic involvement. When diffuse hepatic involvement occurs, reviewers should use their expert judgment to decide whether the liver can be used as a reference organ, though the TFs were not able to provide an alternative organ reference tissue in this scenario because of lack of available publications on the matter and the rarity of the circumstance.

In areas with high physiologic uptake, uptake higher than liver uptake may not always preclude the assessment of a CMR, such as in the Waldeyer ring or in extranodal sites with high physiologic uptake (e.g., gastrointestinal tract or esophagogastric junction) or with activation within the spleen or marrow (e.g., with chemotherapy or granulocyte colony-stimulating factor).

New Nodal Lesions and Regrowth of Nodal Lesions on CT

In addition to the size threshold (i.e., >15 mm in the longest transverse diameter), it is recommended that a 5-mm absolute increase from nadir be applied to declare new or recurrent nodal lesions. It is also recommended that care be taken when assessing progression in small nodes for which limited variation in size may represent physiologic or posttherapeutic changes (e.g., nodes replenished with B cells months after discontinuation of anti-CD19/20 therapies) to avoid overcalling progression due to small size variation.

Discordance Between Splenic and Nodal Disease Outcomes

In cases of nodal response but unequivocal new or recurrent splenomegaly presumed due to lymphoma (e.g., with ^{18}F-FDG uptake on PET/CT, suggestive of lymphoma involvement), it is recommended that disease progression be reported. Conversely, in situations in which FDG-avid lymphomas have sustained splenomegaly on CT without ^{18}F-FDG uptake higher than in normal liver but complete resolution of ^{18}F-FDG activity in nodal tissue, a CMR (and thus an imaging CR) may be declared per the Lugano classification. Additionally, consideration of other conditions that may cause a diffuse increase in organ ^{18}F-FDG uptake is suggested since several pharmaceutical products (e.g., granulocyte colony-stimulating factor) or other treatments given to support blood counts may increase splenic activity.

Further recommendations for the evaluation of the spleen and nodes can be found in the supplemental materials and Supplemental Figures 2–5. Summary tables of recommendations can be found in Supplemental Table 2.

CONCLUSION

The PRoLoG initiative has created a platform to gather recommendations from an international group of recognized imaging and clinical experts from industry and academia in the field of lymphoma response assessment to standardize application of the Lugano classification in clinical trials and beyond. These recommendations are intended for clinical users at local sites and central facilities in academic and pharmaceutical clinical trials and should be used as a companion to the Lugano classification to enhance assessment of response and facilitate clinical trial conduct and regulatory review, ultimately leading to improved lymphoma patient outcome.

DISCLOSURE

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KEY POINTS

QUESTION: How can the Lugano classification be consistently applied among clinical end users?

PERTINENT FINDINGS: These consensus recommendations should be used as a companion to the Lugano classification with regard to the FDG avidity of different lymphoma entities, response nomenclature, lesion classification, and scoring. Response assessment; use of clinical data; and spleen, liver, and nodal evaluation are clarified.

IMPLICATIONS FOR PATIENT CARE: This guidance will enhance use of the Lugano classification, facilitating clinical trial conduct and regulatory review and ultimately leading to improved lymphoma patient outcome.

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