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How can the WHO classification framework for hematolymphoid neoplasms be updated in future versions to accommodate the multiple demands it faces?

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The WHO classification of hematolymphoid neoplasms currently serves several purposes: guiding reproducible diagnosis worldwide, providing a biologically grounded framework for disease classification, informing treatment, supporting clinical trials, and enabling population-level surveillance (1, 2). Although these functions overlap, fulfilling all of them across all settings is exceptionally challenging. Integrating multiple purpose-specific classification systems within a layered WHO framework may help address demands that a single hierarchical classification system cannot fully meet. Although this approach would represent a substantial change and may not be feasible in the near term, it merits consideration. To explore its potential value, it is useful first to examine the challenges facing the current framework.

1) The diagnosis of hematolymphoid malignancies requires an integrated approach incorporating clinical, morphological, immunophenotypic, immunohistochemical, and genomic features. However, diagnostic resources and access to diagnostic services are not equitably distributed worldwide or even within individual countries. Well-resourced centers may exist in low- and middle-income countries, while some patient populations in high-income countries may be unable to afford optimal diagnostic investigations. As an increasing proportion of WHO entities are defined by genomic or other molecular features, universal implementation of the WHO classification remains a major challenge (3, 4). The current distinction between “essential” and “desirable” diagnostic criteria does not adequately address this challenge. This dichotomy may also constrain the practice of precision oncology and impede scientific advancement.
2) The WHO’s hierarchical classification uses umbrella terms encompassing multiple entities, allowing a broader designation when diagnostic constraints preclude assignment to a specific entity. However, this strategy may not adequately address situations in which resource limitations prevent the distinction between entities with markedly different clinical outcomes and treatment requirements. Examples include distinctions among entities within the broad “large B-cell lymphoma” category (5).
3) Even in well-resourced settings, a patient’s comorbidities and frailty may limit treatment options at diagnosis, reducing the immediate need for greater diagnostic precision and the investigations required to achieve it (6). However, the patient’s clinical condition and the need for diagnostic precision may change over time. In addition, training and translational research needs at academic institutions may influence the scope of diagnostic investigations.
4) Genomics has substantially advanced our understanding of disease. However, there is a tendency to recognize new entities on the basis of relatively small datasets and inadequate comparator groups. Although such studies are valuable for generating hypotheses for further investigation, the premature incorporation of these entities into disease classifications risks relying on insufficient evidence (7).

5) Treatment response depends on the therapy administered, disease biology, and patient-related factors. New therapies can transform a disease associated with poor outcomes into one with favorable prognosis. Prognostic stratification is therefore context dependent and may change over time; it should not serve as the basis for defining disease entities.
6) Existing clinical trials and patient management strategies can also pose barriers to revising disease classifications, although the impact of such revisions has been shown to be limited (8).
7) A major remit of IARC, which oversees the WHO classification, is to support epidemiological research and cancer registries. Introducing new entities or revising existing ones can affect these activities.

What might a revised approach look like?

a) Ideally, the framework would include two complementary sets/lists of diagnostic entities. The first would comprise entities that can be reliably diagnosed in resource-limited settings (limited-diagnosis category). This set could also be used in well-resourced settings when patient-related factors, such as frailty, comorbidities, or affordability together with the practice context, limit treatment options. The second would comprise entities that reflect contemporary understanding of disease biology and are supported by robust evidence (optimal-diagnosis category).
b) Develop a separate list of candidate entities proposed for recognition as distinct from those included in the “optimal-diagnosis category.” These candidates should be regarded as hypothesis-generating and documented separately pending further supporting evidence. A transparent framework should also be established to define the level of evidence and the pathway required for recognition as a distinct entity. The “optimal-diagnosis category” should include holding groups for pathologically similar conditions whose underlying biology remains incompletely understood, with a defined framework for their further investigation and subdivision as evidence emerges.
c) For each entity in the “optimal-diagnosis category,” an evidence-based, consensus list of treatment-independent and treatment-dependent prognostic and predictive factors should be developed and continually updated to reflect emerging evidence.
d) The diagnosis should also include the most appropriate ICD-O code. The system should also include a mechanism to flag cases for which no exact code exists, enabling retrospective recoding when an appropriate code becomes available. Similarly, diagnoses assigned to entities in the “limited-diagnosis category” should be explicitly flagged.

e) A more considered approach is needed to address discrepancies between the recognition of new disease entities or terminologies (candidate entities and holding groups) and eligibility for enrollment in clinical trials. A universally accepted mapping of such entities/groups to the diagnostic categories used in clinical trials should be established and applied unless a trial protocol specifies otherwise. This would help prevent changes in disease classification from inadvertently restricting trial eligibility.

In resource-limited settings, the diagnosis should specify the applicable entity from the “limited-diagnosis category,” together with the most appropriate ICD-O code and a flag indicating the relevant contextual constraints. In other settings, the diagnosis should specify the applicable entity from the “optimal-diagnosis category,” together with the most appropriate ICD-O code and the agreed-upon prognostic and predictive factors.

When a candidate entity or holding group is identified, the diagnostic report should document this designation alongside the most closely corresponding entity in the previous edition of the WHO classification and its ICD-O code, with a flag indicating the potential need for retrospective recoding. Comments may also describe less well-established prognostic and predictive factors and any implications for clinical trial eligibility.

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