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Editorial Comment

Cancer taxonomy: pathology beyond pathology

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Abstract The way we categorise and classify cancer types dictates not only the way we diagnose and treat patients but also many of our decisions on biomarker and drug development. In addition, cancer taxonomy proves the ground truth for future discoveries in the area of computational pathology and artificial intelligence.

This editorial comment illustrates the relevance of cancer taxonomy in clinical and morpho-molecular diagnosis, prognosis and therapeutic prediction; it shows its importance in identifying the epidemiology, aetiology and pathogenesis in oncology and explains its determinant role in computational tissue-based cancer diagnosis.

For many decades, pathologists have been the real taxonomists of cancer. Since the 1st edition, edited by Dr. Leslie Sobin for the World Health Organisation (WHO) and published by the WHO in Geneva in 1967–1981 [1], the WHO Classification of Tumours (usually known as the 'WHO Blue Books') has been the reference for the classification of cancer worldwide. With the first book of the 5th edition of the WHO Blue Books in the later stages of production, it may be pertinent to reflect about the role of cancer taxonomy in the era of molecular medicine and the promise of pathology digitalisation and artificial intelligence applications to routine diagnostics. A summary of the relevance of cancer taxonomy is depicted in Fig. 1.

1. The value of cancer classifications

A single, unified classification of cancer not only is required for standardized diagnosis, but also is paramount to frame the way we understand cancer and we deliver and improve oncology care internationally. Having a single cancer taxonomy is essential at many levels: to monitor cancer incidence, understand cancer epidemiology, explore the aetiology and pathogenesis of

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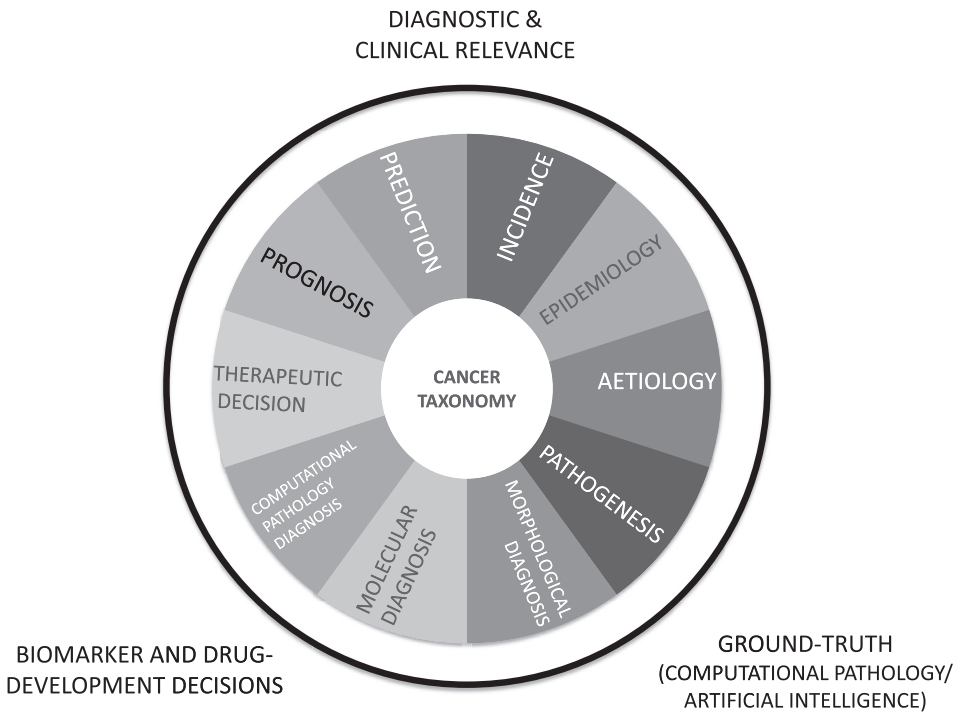

Fig. 1. The relevance of cancer taxonomy in modern medicine.

neoplasia, improve diagnostic criteria, focus therapeutic decision-making, define cancer prognosis and, crucially, begin to elucidate the predictive response to therapeutic intervention.

The referential value of an authoritative and widely accepted cancer classification, however, transcends these immediate practical applications. Cancer classification frames the activity of translational research, dictating research activity and therefore the disparity in resource availability by national agencies and large charities to different cancer types. For instance, 'rare cancers' are defined as having an incidence rate of less than 6 per 100,000 individuals per year [2]; indeed, this explains the little interest of scientists in these cancer types that, individually, are not career makers. The low frequency of these cancer subgroups and hence the perception of modest returns also govern the discussion on healthcare economics, focussing drug industry development decisions away from them [3]. Overall, the lack of interest in biomarker and drug development in these areas, with important but isolated exceptions such as imatinib for the treatment of gastrointestinal stromal tumours, denies significant improvements in personalized medicine to a group that, as a whole, includes around 200 'taxonomy entities' and makes up for 20–25% of all patients with cancer [4].

2. Ground truth and artificial intelligence

In addition, a new and important responsibility is beginning to be placed upon the pathological description of cancer 'entities'. The efforts of artificial intelligence and digital pathology today to create algorithms and tools for better diagnostics require a 'ground truth' to refer to [5]. This ground truth needs to be robust, thus describing cancer subgroups that are defined on clear practical grounds, without which the application of an analytical *armamentarium* that includes multiple convolutional neural networks, autoencoders or generative adversarial networks becomes meaningless. More than ever, the traditional controversy among pathologists between 'lumpers' and 'splitters' is alive [6]. The robustness by which we define 'entities' that are then accepted as 'cancer types' needs therefore to be revisited, if we still wish the pathological ground truth to be the reference for artificial intelligence (AI) tool development.

3. Diagnostic affordability and cancer classification

The history of the evolution of the Blue Books does also reflect the change in our perception of cancer over the years. Although in some organs the classification exercise is still predominantly morphological [7], other classifications have been significantly transformed by the introduction of robust molecular information [8,9]. However, in many cancers, we still have subtypes defined predominantly by grading (prostate cancer Gleason 7) [10] or staging (stage 2 colorectal cancer) [11], where good and bad prognostic subgroups exist, for which, to date, there are no widely acceptable morphological or molecular classifiers to guide

prognosis or therapy. This tendency to expand the complexity in the disease classification also leads to an increase in global healthcare disparities. For instance, a classification of glioma that requires careful histological description, a battery of single molecular tests and a high-throughput methylation analysis with complex bioinformatics curation [8] will not be available to many laboratories worldwide. Should classifications accept a 'universal' common denominator available to all through affordable tools and acquirable knowledge? Or should we embrace complex, detailed (and thus less affordable) genomic tools in this exercise? The issue of economic disparity also questions the grounds in which sometimes we approach some classifications. Should we accept, for instance, that the molecular classification of lung adenocarcinoma (with strong therapeutic implications) [12] is superior to a morphology predominant one [13]? And should this still be the case if some of these holistic molecular diagnostic approaches are not affordable worldwide?

4. What is a new 'entity'?

It appears, therefore, that the question of 'What represents a new entity?' in cancer classification at this point of the 21st century has a relevance that goes well beyond the simple discussion of morphological characteristics. When should a new entity be adopted by international expert panels such as the WHO Classification of Tumours Editorial Board? The question is complex, and it is likely that a single set of rules may not be able to present a clear-cut distinction between an interesting observation and a proper disease entity. However, it would appear that the latter should satisfy at least some of the following principles, namely, (a) significant number of cases describing the entity: the precise number of which may differ depending on the wide or restricted nature of the entity, but should perhaps a minimum be incorporated? (b) adequate number of independent studies reporting the entity; (c) practical utility of the proposed entity because of its clinical relevance or uniqueness; (d) unique biological background—there is a mutation, transcriptomic signature or specific immunohistochemical profile that is characteristic (perhaps pathognomonic) of the proposed entity and (e) in the future, artificial intelligence approaches, which may improve or perhaps contradict existing established paradigms, may lead to a unique definition of the entity in question.

Without objective and measurable features, the diagnosis of cancer remains today, in many instances, a subjective morphological opinion and hence is subject to change. Importantly, a change in established taxonomical principles accepted globally may have significant implications and may need to be managed carefully. For instance, let us consider a potential change in the classification of dysplasia in a certain organ system. It is likely that, if clinical accessibility is possible, there may be international, detailed, lengthy and longitudinal screening programmes, which have adopted the previous classification of dysplasia as a decision maker in the screening programme's pathway. As such, it would appear that detailed tables of equivalence and transition periods may be necessary for the adoption of a new classification, as well as (for some tumour types) a hierarchy of classification with may go from simple to more complex diagnostic armamentarium available to only a few in high-income countries.

5. Who should be the taxonomist?

If taxonomy is becoming such a complex exercise, a final question remains to be addressed. Are pathologists still the best people within the scientific community to be trusted in driving the discussions on cancer taxonomy? At this point, expert pathologists are still in the best position to understand the aetio-epidemiological, physiopathological, morphomolecular, computational and clinical dimensions of disease. However, the WHO Blue Books do now involve other clinical experts as editors and authors as necessary. Will the pathology community be able to train 'the pathologists of the future' to play a central role in the diagnostic and therapeutic decision-making and continue to drive the taxonomy of diseases? This possibly represents one of the most important challenges for the practice of a pathologist in years to come [14].

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Conflict of interest statement

None declared.

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