EDITORIAL

Here Comes the SUN (Part 2): Standardization of Uveitis Nomenclature for Disease Classification Criteria

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Nosology…is not a sport for the timid.
—Sherwin B. Nuland, MD[1]

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In this issue of AJOPHT, the Standardization of Uveitis Nomenclature (SUN) Working Group, under the leadership of Douglas A. Jabs, presents the results of a monumental, decade-long effort to define classification criteria for a wide range of uveitic conditions.[2-27] Such an endeavor has rarely been attempted in modern medicine and has not been undertaken previously in any major subspecialty of ophthalmology. The project consisted of collecting described cases (using specific descriptor terms) from a large group of uveitis specialists, determining expert consensus on features of canonical cases, and defining classification criteria based on these, followed by validation on a hold-out set of cases using machine learning techniques. The end results are criteria that can be used to define specific uveitic conditions in order to standardize future clinical studies.

An analogy may be useful to make the problems and methods more accessible. The members of the World Association of Canine Kennel Owners (WACKO) need to understand if one particular dog treat is more effective than others in training certain breeds of dogs. Some breeds are readily distinguishable: no one would confuse a Great Dane with a Chihuahua. But other breeds are easily confused, for instance, the Alaskan Malamute and the Siberian Husky. How can WACKO develop clear criteria for distinguishing these breeds? The group decides to use its consortium to find consensus. Each member is asked to submit descriptors of her or his dogs for specific breeds (ie, hair length, snout shape, tail curl, and so forth), along with pictures if available. Panels of WACKO breed experts review the cases and come to agreement on cases which fit their criteria for which dogs belong to a specific breed. The descriptors are then summarized, and critical descriptors that define breeds uniquely are identified (ie, a Malamute's tail curls over its back, whereas a Husky's tail does not). The criteria are then validated on a held-out set of dog descriptions, where a machine learning algorithm trained on the consensus cases is used to identify the breed based solely on the description. The WACKO consortium then agrees to use these criteria going forward in their studies of responses to training treats, comparative obstacle course performance of dog breeds, and any other studies requiring definitions of breeds.

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Why apply this approach to ocular inflammatory disease? Uveitis has always presented unique challenges for diagnostic and classification criteria. The term uveitis describes a heterogenous group of more than 30 clinically distinct conditions with the common feature of intraocular inflammation. However, these conditions may differ by primary site of inflammation within the eye (eg, anterior, intermediate, posterior, and panuveitis); or on the presence or absence of associated systemic immune mediated diseases (eg, juvenile idiopathic arthritis, sarcoidosis); or whether they are infectious or non-infectious. The precise diagnosis, when one can ultimately be made, relies on clinical features and, in some cases, laboratory assessment.[28] For some conditions (such as acute retinal necrosis syndrome) robust diagnostic criteria are available.[29] For others, such as the "white dot" choroiditides, expert opinion still diverges as to the definitions and distinctness of specific conditions.[30] As with our dog analogy, some forms of uveitis are quite distinct (it would be difficult to confuse Fuchs uveitis syndrome [also known as Fuchs heterochromic iridocyclitis] with Vogt-Koyanagi-Harada syndrome), whereas others are extremely difficult to distinguish (for instance acute posterior multifocal placoid pigment epitheliopathy [APMPPE] and persistent placoid maculopathy[31]). In 1996, Rosenbaum and Holland[32] highlighted this problem in their survey of the American Uveitis Society members through case vignettes, where they showed broad disagreement as to appropriate use of fundamental terms such as panuveitis, retinal vasculitis, and posterior uveitis. Their survey highlighted the level of disagreement in terminology and disease descriptors among uveitis experts and emphasized the need for establishing widely accepted definitions and criteria.

The first step in forming consensus is to agree on language. Prior to 2005, there were no broadly agreed-upon definitions for critical and basic descriptors of uveitis such as degree of anterior chamber cell and flare. In that year, the results of the first consensus workshop by an international working group of 45 uveitis experts (the Standardization of Uveitis Nomenclature [SUN] Working Group) was published.[33] This initiative was endorsed by 3 major uveitis organizations (the American Uveitis Society, the International Uveitis Study Group, and the International Ocular Inflammation Society) and was the first comprehensive and systematic effort toward standardization of nomenclature in uveitis. The workshop resulted in consensus on basic diagnostic terminology, inflammatory grading systems, and outcome measures. The terms and measurements endorsed by the first SUN workshop have been adapted by many studies and clinical trials; to date the report has over 1,500 citations.[34] However, the initial effort, while extremely useful, lacked specific disease descriptors and criteria for diagnosis or classification of specific disease entities. Diagnostic criteria are a set of symptoms, signs, or laboratory findings that help clinicians establish diagnosis and make treatment decisions. The primary purpose of disease classifiers, on the other hand, is to identify patients with similar disease features for studies. Depending on the individual disease entity, diagnostic criteria tend to favor sensitivity over specificity in order not to miss a therapeutic opportunity, whereas disease classifiers favor specificity in an attempt to keep a particular study population more homogenous.

Recent advances in molecular diagnostic technologies and the advent of more specific immunomodulatory therapies such as the "biologic" drugs over the last 2 decades has provided unique opportunities to understand underlying mechanisms of uveitis and to advance its treatment. There has been a resultant surge in clinical trials in uveitis. However, many trials have been hampered by heterogeneity in disease features both across and within distinct disease groups, as well as a lack of stringent classification criteria and meaningful outcome measurements. For instance, 3 separate clinical trials for the anti-interleukin 17A biologic agent secukinumab failed to meet the endpoint despite signals in the data suggesting success in subgroups[35,36]; it is possible that disease heterogeneity in inclusion criteria (all "non-infectious posterior and panuveitis") contributed to this failure. Thus, there is a pressing need for more precise disease classification within uveitis.

The SUN Working Group was re-convened in 2009 to develop classification criteria for 25 uveitides using a formal approach. The project proceeded in 4 phases: 1) informatics; 2) case collection; 3) case selection; and 4) machine learning.[37] Between 2010 and 2016, the group developed a standardized case report with predefined descriptors and definitions for case collection and collected information from 76 investigators on 5,766 cases of 25 of the most common uveitides, resulting in an average of approximately 250 cases per disease entity. Laboratory data, fundus photographs, angiograms, and optical coherence tomograms were also collected in relevant cases and were evaluated by case selection committees as well as the independent reading center. Cases were reviewed and approved or rejected by committees of 9 investigators for inclusion into the final database. Cases with supermajority agreement on the diagnosis were selected for identification of classification criteria and validation through machine learning. Machine learning was performed by randomly separating the final dataset into an 85%-15% training and validation set, respectively, for each uveitic class. The results of this effort, compiled in 26 articles in this issue,[2-27] show high classification accuracy that ranges between 92.1% and 99.8% within each disease group, both in the training and the validation sets. Importantly, a masked examiner's evaluation also showed high accuracy rates and was on par with the machine learning classifications.

Although these results are impressive, there are limits to this approach. Strict definitions of descriptors were not validated; for instance, how are "round" and "mutton-fat" keratic precipitates distinguished, and how reliable is this distinction? Neither diagnostic testing nor imaging protocols were standardized. For example, necrotizing retinitis in the context of an HIV patient with a positive treponemal

test could be a viral retinitis or acquired toxoplasmosis, or could be syphilis-related. Definitive diagnosis in that case would require molecular testing of intraocular fluid; but, as testing intraocular fluid is not a requirement for classification of each of these 3 entities, there is the possibility of misclassification. It is notable that 30% of submitted cases were excluded as they did not meet supermajority agreement; these were cases where one expert clearly believed a case met criteria where the expert panel did not. Although use of small committees for consensus is optimal for efficiently adjudicating cases while also supporting a diversity of opinion, the reproducibility of committee decisions was not established, either within a committee (eg, would the same case presented twice be judged the same?) or between committees (eg, would 2 expert committees agree on all cases?). The tendency of such groups is (appropriately) to create restrictive criteria that characterize canonical cases. This may result in overly restrictive criteria; for instance, under the new SUN classification criteria, no purified protein derivative (PPD)-positive patient can be diagnosed with sarcoidosis-associated uveitis. Given that one-third of the world's population is PPD-positive, either from latent tuberculosis[38] or cross-reaction from Bacille Calmet-Guerin vaccination [39] (used in much of the world), these criteria could hinder enrolment in clinical trials for sarcoidosis-associated uveitis in many countries.

The overall approach for machine learning was to perform a lasso-regularized, multinomial multivariate regression for each of the uveitic diagnoses to develop a multiclass classification. The trained model was then used to develop a set of Boolean expressions that could fully describe the classification of each disease. The great advantage of taking this approach is that a fully explainable and interpretable model is developed. In contrast, using random forests, support vector machines, or deep learning networks would not lead to the same level of transparency. Although accuracy and misclassification rates can be misleading in unbalanced datasets, overall this kind of "white box" approach in medical artificial intelligence aids in adding face validity with the criteria and failure analyses in the future.

However, it is not clear that the current machine learning paradigms are optimal. While these approaches yield specific classification rule sets for each disease, many different machine learning models can be unwieldy to implement and use in practice. When a new patient is seen in a clinic, all potential disease models would need to be run in parallel, and these results could yield conflicting or confusing results. Furthermore, the current machine learning assumed correct classification of uveitis into an anatomic subgroup (ie, machine learning for anterior uveitis was validated only against other anterior uveitis diagnoses). As Rosenbaum and Holland[32] showed, there may not be clear consensus on even this distinction. A prospective validation and implementation study using these models and criteria would greatly enhance this body of work and may represent an important future study.

Other challenges and opportunities also await. The use of descriptors entails human feature extraction and necessarily may be subject to variance or error. In the future, machine learning approaches could be used to perform classification based solely on objective data such as visual acuity and intraocular pressure measurements, anterior chamber optical coherence tomography, and cell analysis, optical flare analysis, and wide-field fundus imaging. Unsupervised clustering analyses of such data could yield insights into diseases where distinctions are arbitrarily imposed on continuous disease spectra or where a distinct subset of cases has been lumped into a larger category. Maintaining currency is also a substantial challenge for this system. As new knowledge results in changes in disease classification, how can these criteria be updated and re-validated? This will be a particular challenge as new clinical or laboratory testing modalities are incorporated into clinical practice. As well, the SUN efforts are not unique. Working groups have proposed diagnostic and classification criteria for a variety of conditions also considered by the SUN group, including Vogt-Koyanagi-Harada disease,[40,41] ocular sarcoidosis,[42,43] Behcet disease,[44] and tubercular uveitis.[45] Although some of these aim for diagnostic rather than classification criteria, it will be challenging in practice to manage multiple validated criteria that may not be consistent.

Finally, in applying the results of this huge effort, it is important to emphasize the distinction between the classification criteria introduced by the SUN Working Group, which are mainly intended for use in clinical research and clinical trials, and diagnostic criteria that are intended for clinical practice. It must be emphasized that the SUN classification scheme is designed and applicable only for selection of cases for clinical studies. Although this is an exciting first step to confront this challenging area, the ascertainment issues of cases in the study may result in a classifier that works well on cases that that meet the uveitis expert "consensus agreement" and does not generalize well to "real world cases." These criteria are not meant for a routine clinical diagnosis (any more than breed characteristics can be applied successfully to mutts). The process of standardizing the approach to disease diagnosis, classification, and outcomes that account for the obvious heterogeneity in disease features and aims for a set of descriptors to create a homogenous cohort of "most representative" of a disease category is certainly a step in the right direction. However, the future will likely demand more precise and biologically relevant classifiers as the field of medicine moves away from classifiers based on clinical phenotypes and moves toward classifiers based on underlying mechanisms. For the present and near future, however, the results of this SUN project will doubtless be applied to most large clinical studies in uveitis, and will provide a level of rigor the field has not previously enjoyed.

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