

# Do We Have Blind Spots in Our Diagnostic Vision?



The development of procedures for identifying cases of any disease entity necessarily has to start with collecting patients that have features in common clinically. Thus, forming a cohort defined by common clinical findings and distinct from other patients without these findings is the first step towards diagnostic or classification criteria, which can be tested formally for specificity and sensitivity and validated in various populations. This is common knowledge in the rheumatological community worldwide: we use such sets of criteria every day, either formally or as a pedagogical aid when performing our art of medicine.

But if patients in the community are not from a population compatible with the cohort used for criteria construction, we might have a problem. This disparity has not been obvious, but is highlighted by Michael M. Ward in this issue of *The Journal*<sup>1</sup>. Ward's article concludes that, "The finding that patients with SLE hospitalized at academic medical centers have more severe illness than those at community hospitals has severe implications for interpreting results from studies performed at academic medical centers. Observational studies of patients' outcomes may not be representative of the outcomes of patients seen in community settings. In addition, the generalizability of case-control studies, studies of diagnostic test performance, and controlled trials may also be affected"<sup>1</sup>.

Criteria for classification and more rarely for diagnosis have been developed and validated for most rheumatic diseases and eventually adopted by the American College of Rheumatology (ACR). It has been said that conceptually no difference exists between classification criteria and diagnostic criteria<sup>2</sup>, a statement that should be interpreted with caution since the purpose of these criteria differs. Differently retrieved cohorts are obviously needed for development of the 2 kinds of criteria, a fact stressed by Ward's findings.

Indeed, most if not all the criteria we use for diagnosis or classification are developed in academic medical centers. Are these criteria adequate for identifying patients in community settings? The answer is: We don't know. Our criteria

are generalized and doctors all over the globe, not only in academic settings, are identifying patients that correspond to the original cohort in the academic settings where the criteria were developed. Are there patients in the population with the same etiology, often unknown, the same disease mechanisms — maybe with a slightly different clinical presentation — that are not being identified and classified due to blind spots in our diagnostic vision? Again, we don't know, but we think the issue must be addressed. And finally, there might be important differences and blind spots between doctors from different specialties, also within academic centers.

In the literature we can find many indications that the blind spots are there. We can illustrate this with various articles on systemic lupus erythematosus (SLE), to extend the observations by Ward. When starting the SLE International Collaborating Clinic's (SLICC) validation of disease activity measurements, we realized in an early phase that with the same instructions to pick 10 patients with SLE in each center we ended up with very different patient contributions. This comparison between international academic centers illustrates that even within this setting, using the same classification criteria can result in differing spectra<sup>3</sup>.

In the LUMINA cohort from Alabama, USA, it was observed that patients of African-American ethnicity who were poor and younger had more active SLE<sup>4</sup>, and those who did not come for visits also lived closer to the center<sup>5</sup>. These are all factors that might affect where patients are seen within the healthcare system. In addition it has been shown from North Carolina, USA, that African-American patients differ in clinical presentation from white patients<sup>6</sup>, which of course might affect the identification of cases in both ethnic groups. In the LUMINA cohort, patients diagnosed with SLE according to criteria, but who had symptoms of fibromyalgia, seem to represent another entity, not properly defined with existing criteria<sup>7</sup>. In the same cohort it was also shown that accrual of ACR criteria for SLE is very varied, but that Texas Hispanics have a more rapid evolution of criteria than other ethnic groups<sup>8</sup>. Along the same

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lines it has been reported from Oklahoma, USA, that African-American men are diagnosed with SLE more rapidly than females or other ethnic groups. The early occurrence of nephritis in this subgroup is suggested to be the reason for early detection<sup>9</sup>.

To address the inclusion problems highlighted in this editorial, Costenbader and colleagues recently proposed the use of the Boston weighted criteria and showed that more patients were classified with these criteria than with the crude ACR criteria<sup>10</sup>. But this approach was also based on an academic setting and may not be generalizable.

The other side of the coin indicating existence of blind spots is the diagnostic entity of undifferentiated connective tissue syndromes, proposed by LeRoy in 1980<sup>11</sup>. This spectrum of syndromes, often not developing into more defined disease but with many mechanisms in common with such disorders, might represent to some extent the misuse of classification criteria from academic settings for diagnostic purposes. Such misuse would not correctly identify early disease, let alone non-classical syndromes. We have blind spots again!

Previous work by Ward illustrates other interesting aspects that might add information to why patients in academic centers differ from patients in community hospitals. Apart from referrals, patients also might migrate for health care<sup>12</sup>, and mortality among patients with SLE varies with the experience a hospital has in treating patients with SLE<sup>13</sup>.

Obviously, we have to develop diagnostic or classification criteria for the intended populations. Speaking of SLE, we might even need different criteria in different ethnic groups, maybe in different age groups, and so on. If criteria are to be applied in community settings we have to show that they are effective there. The best way to accomplish this would be to develop them from cohorts collected in community settings with unselected patients. The second-best alternative would be to study the performance of existing criteria in unselected settings, with the obvious risk that we would find that several of our criteria sets are not valid.

The primary object of classification criteria is to discriminate the target disease from other diseases, and the secondary object, to separate individuals with the target disease from healthy subjects. Thus, the frequency of the clinical and laboratory items characteristic of the target disease should be compared with the frequency in other relevant defined clinical disorders and eventually also in healthy controls. It is crucial that relevant contrast/control groups are chosen. Ideally, disease categories that are common in the differential diagnosis of the target disease should be included. Since classification criteria should discriminate between clinically related disorders, the primary requirement for inclusion of items is a high degree of specificity, while for classification purposes sensitivity is a secondary requirement. Classification criteria based on patients with advanced, established disease are criteria that could be and have been developed in academic settings.

Diagnostic criteria, on the other hand, should be constructed for and tested on patients retrieved in a diagnostic situation, that is, with early disease. Clinical and laboratory items used for diagnosis are identified by consensus, and the occurrence of predetermined features should then be analyzed in individuals with possible disease. To avoid diagnostic bias these patients should be *de novo* primary care patients, and not previously selected by diagnostic procedures administered by specialists. Since diagnostic criteria should identify all individuals with the studied disease within an unselected population, a high degree of sensitivity is required.

To accomplish criteria sets that are useful in the clinic is obviously a cumbersome task. According to the important message in Ward's article we have to put more effort into choosing the right settings both for developing criteria and when planning studies. However, this hard work might be worthwhile since further progress along these lines would eliminate blind spots and improve our vision. Perhaps there is something great on the landscape out there, which we simply cannot see today?

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