Response to: ‘Why CAPS criteria are not diagnostic criteria?’ by Landewé and van der Heijde

It is a great privilege for us to send this response to the letter submitted by Landewé and van der Heijde, who are high-profile leaders in the development of classification criteria for the European League Against Rheumatism (EULAR). We thank them for their kind and educational comments.

Cryopyrin-associated periodic syndrome (CAPS) is a rare and clinically heterogeneous disease. As masterfully put together by Toplak et al. in 2012, the delay to diagnosis of CAPS—due to lack of recognition and/or lack of access to the gold standard test, the confirmation of disease causing mutations in the NLRP3 gene—results in a tremendous disease burden. While being undiagnosed and untreated, the systemic inflammation of CAPS results in irreversible skeletal deformities, developmental delay due to hydrocephalus, hearing loss and renal failure.

Children and adults with CAPS have the right of an early diagnosis, as do the many others with rare, under-recognized diseases for which no criteria exist. Only a confirmed diagnosis—not a classification—gives patients access to effective, but expensive medications. While classification criteria aim to identify homogenous cohorts for research studies, diagnostic criteria enable a diagnosis of a heterogeneous disease. This is exactly where the international team of CAPS experts started, frustrated by the ongoing significant delay to diagnosis prohibiting initiation of effective therapies and prevention of irreversible organ damage secondary to inflammation. Some of the team members work in centres like the US National Institute of Health with easy access to genetic testing, while others continue to struggle with significant barriers for advanced diagnostics including the gold standard of mutation testing. Together, we built a framework that enables the diagnosis of CAPS largely independent of the wealth of the healthcare system. We were delighted to learn that it has very similar characteristics when applied to mutation-positive and mutation-negative patients with CAPS.

As pointed out by Aggarwal et al., the development of a comprehensive set of clinical criteria and laboratory markers is the hallmark of diagnostic criteria. In fact, the development of the proposed criteria was discussed with leading experts of classification frameworks in rheumatology on both sides of the Atlantic. They were encouraging, yet felt to be outside the mandate of both EULAR and the American College of Rheumatology (ACR). While the CAPS criteria development methodology had clear overlap with the current ACR/EULAR framework, the validation of the proposed CAPS diagnosis criteria was distinctly different from approaches taken for the development of classification criteria. While classification criteria are commonly validated within cohorts of patients with the disease of interest resulting in high sensitivity and specificity, the group validated the diagnostic criteria in a large cohort of children and adults suffering from true mimics of CAPS at the time of diagnosis—systemic inflammatory diseases. This led to a lower, yet ‘real-life’ sensitivity and specificity. As Landewe and van der Heijde kindly calculated, the criteria are not perfect and will still ‘undercall’ CAPS. However, we believe they will provide guidance for an early diagnostic evaluation and ensure access to treatment for a significant number of children and adults with CAPS.

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Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

Accepted 23 November 2016
Published Online First 16 December 2016


REFERENCES