**Letter to the Editor**

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**Comment to: Extensive analytical evaluation of the performances of the new DiaSys PCT assay and comparison with Elecsys B·R·A·H·M·S PCT test on Roche Cobas and B·R·A·H·M·S PCT-sensitive Kryptor**

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To the Editor,

With great interest we read the article on “Extensive analytical evaluation of the performances of the new DiaSys PCT assay and comparison with Elecsys B·R·A·H·M·S PCT test on Roche Cobas and B·R·A·H·M·S PCT-sensitive Kryptor”, recently published in Clinical Chemistry and Laboratory Medicine [1].

The authors present the deep analytical performance evaluation of the PETIA-based procalcitonin test by DiaSys Diagnostic GmbH (Holzheim, Germany), investigating the main analytical parameters (LOQ, linearity, precision, and sample method comparison). The DiaSys PCT assay was reported to have good analytical performances and good agreement with the B·R·A·H·M·S-licenced methods by Roche Diagnostics GmbH and Thermo Scientific at concentrations ≥0.50 μg/L. However, at lower concentrations, the agreement was reported to be poor, and imprecision significantly higher. In this comment, we would like to point out several aspects, which we consider relevant in regard to the reported data and the understanding the importance of the widespread availability of this parameter and its standardization.

The authors in some cases report better assay’s performances than those given by the test manufacturer itself (linearity [80 μg/L vs. 50 μg/L] and limit of quantitation [0.18 μg/L vs. 0.25 μg/L]). On the other hand, they report higher imprecision than that described by previous works [2, 3]. This may be explained by the fact that different protocols have been used to evaluate imprecision (5- vs. 20-day protocol for previous works and the present one, respectively). It seems likely that further variability sources have been encompassed in the present evaluation. Additionally, no information is reported about the PCT concentrations, which the imprecision was measured at, so the comparison with the two B·R·A·H·M·S assays is partially hindered.

The method comparison of the new DiaSys PETIA procalcitonin test shows to be suitable for sepsis diagnosis purposes (cut-off ≥0.5 μg/L), contrary to what previously was reported by the same authors in regard to a PETIA-based immunoassay by a different manufacturer [4] (Figure 1A).

The statistically significant constant systematic error, evident in Figure 1B, could explain the lower medical concordance (Cohen’s kappa) between the tests at concentrations <0.5 μg/L. However, it should be mentioned that this may be ascribable to the lack of commutability for the calibrators [5] more than to the used tests themselves.

The three specific samples, used by Di Deo-Vantaggiato et al., showing a significant difference in PCT quantification by the PETIA test in comparison to the BRAHMS tests, may also deserve a dedicated comment. The associated clinical background or further microbiological analysis of these samples is not provided by the authors. This hinders, as already stated by authors, the final interpretation. The authors state that these samples were stored frozen at −80 °C. The DiaSys procalcitonin test is based on the homogenous PETIA technology, which can be influenced by possible
aggregates forming upon freeze/thawing process. This setting usually does not appear when fresh samples are analysed and may be removed by proper centrifugation.

The authors outline that the three tests (DiaSys, Roche, Thermo Scientific) do employ different antibodies. Especially, the test by DiaSys utilizes polyclonal antibodies. Indeed, these antibodies might have a selective advantage over monoclonal in picking up different PCT isoforms. Monoclonal antibodies additionally may present some restrictions, especially in relation to post-translational modifications, as recently described in the case of PCT [6].

If, as stated by the authors the PETIA presents generally higher imprecision in the range <0.5 μg/L (as expected for a homogenous technology), it should be stressed that it delivers a bunch of other advantages over the heterogeneous assays. First, PETIA has faster time-to-result and higher throughput, since it is applicable to every clinical chemistry analyser and does not need dedicated equipment as the CLIA does. Second, it is accompanied by a more advantageous balance between performance and expenses, what is of particular interest in low or middle-income countries, where 85 % of whole worldwide sepsis cases are detected [7]. Finally, in the view of the laboratory sustainability, as recently published in this Journal [8], the PETIA can offer remarkable benefits, as no disposable material is used (e.g. disposable cuvettes). Furthermore, this technology can be very reliable and did already show good applicability for other important proteins, e.g. CRP [9].

The DiaSys procalcitonin assay's comparability to Thermo/B·R·A·H·M·S Kryptor has been previously published [2], showing a significant proportional error (approx. 15 %). The new data presented by the Di Deo-Vantaggiato et al. contradict what was previously shown, proving no statistically significant proportional error for the DiaSys PETIA assay. The new data seem to show that the DiaSys test has only approx. 20 % higher recovery vs. ROCHE Cobas e801, while the same tests in previous studies were reported to have a pronounced proportional error up to approx. 68 % [3]. This highly heterogenic situation (Figure 2) has been widely depicted in the literature [5, 10] and emphasises the clear need for the standardization and international higher-order reference material. This topic has been accordingly addressed in the last years by the International Federation of Clinical Chemistry (IFCC) Working Group on standardization of PCT assays.

![Figure 1: Comparison of performances in the medical decisional range (0–1 μg/L) for the two procalcitonin PETIA. (A) Method comparison PCT Diazyme PETIA vs. PCT BRAHMS sensitive Kryptor, reported from Ceriotti et al. [4]. (B) Method comparison PCT DiaSys PETIA vs. PCT BRAHMS sensitive Kryptor, as reported by Di Deo-Vantaggiato et al. [1].](image1)

![Figure 2: Representation of the heterogenic situation of procalcitonin measurements in Germany in 2020. Adapted from Masetto et al. [5].](image2)
In conclusion, we think that procalcitonin determination by PETIA, even though less precise in a concentration range <0.5 μg/L, can offer noteworthy advantages for the systemic infection/sepsis application. In our opinion, it should be clearly stated that each assay should be used only for the intended use, which it is designed for. Different clinical applications should be extended by the final user only on own responsibility. In the specific case, the DiaSys’ test is exclusively thought for diagnosis of sepsis/bacterial infection and to guide the antibiotic therapy, not for lower respiratory tract infection (LRTI). Nonetheless, the overall comparability of different procalcitonin technologies and assays should be clearly improved by the establishment of an international reference material and an absolute reference method.

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Competing interests: Thomas Masetto and Matthias Grimmler are employees of DiaSys Diagnostic GmbH and are named as inventors in the international patent application (PCT/EP2021/051577), claiming the manufacturing and use of the PETIA for the quantification of procalcitonin. Both authors are members of the IFCC working group on the standardization of procalcitonin assays (https://ifcc.org/ifcc-scientific-division/sd-working-groups/wg-pct/), aiming to understand the variability of results provided by the different commercially available PCT assays and to develop and validate a reference measurement procedure for PCT absolute quantification by Stable Isotope Dilution Mass Spectrometry.
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References