Letter to the Editor

Sander De Bruyne*, Charlotte Delrue and Marijn Speeckaert

The underestimated potential of vibrational spectroscopy in clinical laboratory medicine: a translational gap to close

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To the Editor,

Vibrational spectroscopy, namely infrared and Raman spectroscopy, has the potential to be a powerful diagnostic tool in clinical laboratory medicine due to its unique ability to perform a reagent-free multicomponent analysis on almost any sample type in a fast, simple, and non-destructive manner. The technique is based on the interaction of light with matter, which results in the absorption or scattering of light. This interaction is dependent on the molecular vibrations and energy levels, which are specific to the molecular sample composition [1]. The resulting spectral information can be used to identify the biochemical composition of samples, thereby providing valuable diagnostic and prognostic information [1, 2]. Nevertheless, most clinical laboratory analyses still rely on spectroscopic measurements in the visible and ultraviolet (UV) range [1]. While this method is well-established and rapidly expanding in the research field, its application in routine clinical laboratory medicine is currently far beneath its potential. This letter aims to highlight the reasons for this translational gap and the potential solutions for overcoming these barriers.

First, it is necessary to weigh the drive for technological development from the research environment to the medical community's specific needs. To date, most vibrational spectroscopy studies have been performed on general-purpose instruments designed for applications in a broad range of fields such as academic research, the pharmaceutical industry, the food industry, and forensic science [3, 4]. Likewise, the spectroscopic instruments are often optimized for the analysis of chemically pure materials and are not necessarily compatible with existing clinical workflows [5]. There is a need for easy-to-use and robust commercial products, that can be adapted to specific clinical applications. To achieve this objective, innovative hardware and artificial intelligence algorithms for data analysis and interpretation should operate in perfect symbiosis [6]. The software should be designed to provide easy-to-understand and transparent results that can be readily interpreted by non-experts in the field.

Moreover, more extensive validation studies with sufficient sample numbers are needed to assess the accuracy, precision, and reproducibility of vibrational spectroscopy in clinical laboratory settings. As reviewers of clinical vibrational spectroscopy papers, we can state that current studies are often hampered by small sample sizes or the absence of adequate (symptomatic) control groups, presumably reflecting the lack of sufficient interaction between clinicians and experts in the field. In addition to extensive validation studies, large-scale clinical trials with clinically relevant statistics are indispensable for assessing the value of spectral applications in the clinical community. It is essential to report the results accurately and standardize the requirements for reporting [5]. A valuable initial step towards achieving this goal is to examine and incorporate the criteria outlined in the Standard for Reporting of Diagnostic Accuracy Studies (STARD) statement [5, 7]. Unfortunately, such trials are often associated with high costs and important medical diagnostic companies need to be on board and engaged in the drive towards targeted and strategic technological development [4]. For example, Dxcover Limited, a clinical stage liquid biopsy company that recently raised $11.9 million, is developing spectroscopic liquid biopsy technology for the early detection of multiple cancers (e.g., brain and colorectal cancers) by employing infrared spectroscopy of circulating pan-omic biomarkers. The company

***Corresponding author: Sander De Bruyne**, MD, PhD, Department of Laboratory Medicine, Ghent University Hospital, C. Heymanslaan 10, 9000 Ghent, Belgium, Phone: +32 9 33 20674,
E-mail: sander.debruyne@uzgent.be
Charlotte Delrue and Marijn Speeckaert, Department of Nephrology, Ghent University Hospital, Ghent, Belgium

has produced compelling clinical evidence demonstrating high accuracy in the detection of stage I and II cancers.

Furthermore, because for each application, the outcome can be influenced by multiple factors, such as the analytical instrument, sample preparation, measurement protocol, and used data (pre-)processing techniques, efforts should be made to reach a consensus on Standard Operating Procedures (SOPs) [4]. In addition, it is critical to document inter-instrument and inter-laboratory accuracy and precision before constructing a large database of reference spectra. Moreover, since a lack of knowledge feeds the level of skepticism, there is a strong need to raise awareness of vibrational spectroscopy in the clinical laboratory community. Therefore, vibrational spectroscopy researchers should also be encouraged to submit their valuable work to clinical laboratory journals instead of purely analytical or specialized vibrational spectroscopy journals, which often suffer from low visibility among clinical lab professionals. However, an important aspect therein is to employ understandable clinical language, for example, by using commonly employed statistical terms (e.g., sensitivity, specificity, and area under the receiver operating characteristic curve) [4].

Once the fundamental scientific and technological challenges described above are addressed, diagnostic and prognostic tools based on vibrational spectroscopy could have the potential to revolutionize our clinical and laboratory systems leading to more efficient public services, significant economic savings and improved patient outcomes [3]. The unique characteristics of vibrational spectroscopy are especially promising for point-of-care applications because integration of this technology into portable battery-powered devices could offer a platform to monitor multiple health parameters, thereby facilitating the creation of bedside technologies for diagnostic and treatment monitoring purposes [1]. While laboratory-grade instruments are often employed in traditional analytical laboratories, portable instruments are commonly used in more demanding environments. For example, out-of-lab analyzers must have the robustness required by ambient conditions, be resistant to vibrations, and have a stable performance in all physical orientations. Therefore, it is necessary to design and engineer spectroscopic systems for specific applications in more diverse environments than lab-only instruments. Despite these potential challenges, portable and handheld spectrometers have been successfully used in a wide range of applications such as quality assurance and quality control of food ingredients, biodiesel analysis, and historical object conservation. Furthermore, based on available data in the literature, it can generally be concluded that out-of-lab analyzers have the potential to provide similar performance compared to their lab equivalents [8, 9]. In addition, it is not unlikely that miniaturized spectrometers, which are specifically developed and adapted for certain medical applications, have the potential to outperform general-purpose benchtop instruments.

In conclusion, vibrational spectroscopy has the potential to be a powerful diagnostic tool for clinical laboratory medicine. However, translation into clinical practice has been limited because of several barriers that require collaborative efforts between researchers, clinical laboratory professionals, and industry partners. The development of medically adapted instrumentation, standardized sample collection and preparation protocols, user-friendly software for data analysis, extensive validation studies and large-scale clinical trials are critical to overcome these barriers and unlock the technique's full potential.

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