Advancements in mass spectrometry as a tool for clinical analysis: Part I

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Editorial

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I would like to take this opportunity to welcome you to the *Clinical Chemistry and Laboratory Medicine* special issue on *Advancements in Mass Spectrometry as a Tool for Clinical Analysis*. The overall goal of this issue is to highlight the application of mass spectrometry (MS) as a powerful tool for clinical analyses. This ambition has been realized in two ways, firstly by showcasing the acceleration of routine MS-based analyses, and secondly by demonstrating the global, cutting-edge work of researchers to facilitate novel and transformative ideas for clinical MS applications.

The presence of MS within the clinical laboratory is neither a novel nor extraordinary concept. MS has been applied across a number of clinical disciplines for decades, with neonatal screening as a notable example of early adoption of MS for medical purposes [1]. Despite this, access to clinical applications of MS have historically been restricted to specialist centers. The consequence of this is that MS has been far from universal in clinical settings, with significant variation across healthcare providers or treatment regions [2]. However, the continual improvement in instrument usability, coupled with the development of increasingly more cost-effective equipment, has facilitated the availability of MS for clinical investigations. This has led to a sustained growth for an interest in clinical MS research, with a 10-fold increase in annual publications in the last two decades (Figure 1).

Innovation in MS has not been limited to instrumentation. With the ambition of promoting MS as a routine measurement tool, there is a considerable drive to refine sample collection techniques in order to decrease the costs and technical expertise required [3, 4]. This has the potential to improve the robustness of in-community sampling, as well as provide rapid and non-invasive approaches to point-of-care monitoring. For these reasons, it is evident that the development and application of MS-based analyses in the clinical laboratory will only continue, with the potential of MS analysis becoming a mainstay technology in all hospitals.

The articles contained within this issue are only a small part of the excellent research that is being performed internationally. This movement is exploring the clinical potential of MS, with novel developments being frequently reported in the scientific literature. This special issue provides thought-provoking and informative additions to this literature, with articles sub-divided to fall within seven main themes. The high volume and quality of manuscripts submitted to this special issue has been exceptional. For this reason, the articles will be published in print across the April and May issues. In Part I we address the three themes discussed below, with a further four themes considered in Part II.

Drug adherence, testing and therapeutic monitoring

MS has established itself as a routine technology for toxicological assessments and measurements of medication adherence and therapeutic response [5]. Therefore, it seems only fitting that we should begin the special issue with this topic. We jump straight into the subject with an elegant review by Prof. Sangeeta Tanna and colleagues [6], in which they discuss the use of chromatographic techniques coupled to MS for the measurement of medication adherence. In this article, Prof. Tanna also pays tribute to her mentor, colleague and co-author, Dr. Graham Lawson, who sadly passed away during the peer review process. Please take time to read the *In Memoriam* section of this paper to celebrate Dr. Lawson's life and career. This review sets the scene for six original research articles. The first continues our theme by addressing the application of high-resolution MS to test adherence and therapeutic monitoring of statins and associated metabolites [7]. We proceed to toxicological screening with two manuscripts discussing the development and application of MS-based assays for cannabinoid testing [8, 9], a series of compounds gaining attention for their proposed therapeutic benefits [10]. Following these is a fascinating investigation into the identification of metabolites of peptide-derived drugs [11]. This article follows a laboratory medicine approach designed for application in sports anti-doping, highlighting a clear translational capability for clinical drug monitoring. Finally, we conclude this section with two

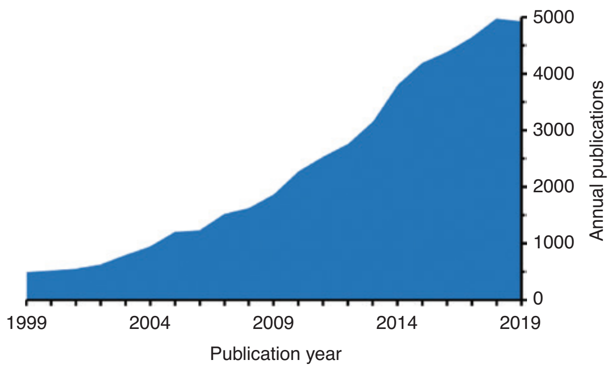

Figure 1: Annual publications indexed in PubMed returned using the search terms 'clinical' and 'mass spectrometry' (search performed 27 January 2020).

studies on drug monitoring that concern the measurement of the anesthetic ropivacaine [12] and the use of ion intensities to improve selectivity for serum measurements of the contrast agent iohexol [13].

Small molecule biomarkers

MS is a recognized technology for the assessment of small molecules (generally <500 Da) that has recently seen a rapid rise in its application to clinical metabolite measurements. Many of the 'biomarker' targets quantitated by MS are metabolic pathway breakdown products which are providing new insight into the impact on processes of health and disease. We begin the largest section of this issue with two papers that discuss the measurement of circulating gut microbial metabolites, currently a topic of intense interest for clinical biomarker investigations [14]. The first article reviews the literature on the use of MS to quantitate bacteria-derived dietary breakdown products, in particular those that have been associated with protective and deleterious associations in disease [15]. Thereafter, the focus shifts on to a single metabolite, trimethylamine N-oxide (or TMAO), to better understand its characteristics and to establish reference values across a generalized, disease-free population [16]. From here, we venture into steroid [17] and hormone [18] analyses, specifically the stability of parent and metabolite molecules within biofluid samples. The studies presented highlight important information regarding the need to correctly process and/or store samples in the hours following collection. Entering the second half of this section, the area of interest becomes the development and validation of MS-based assays and their application to clinical cohorts. This includes the validation of a high-throughput, non-derivatized amino acid screening assay [19] and an interesting application of an alternative ambient ionization setup for measurement of vitamins A and E [20]. Finally, we conclude this theme with applied investigations into biofluid measurements of xanthine oxidoreductase activity [21], serum bile acids in pediatric liver and intestinal disease [22] and glucosylsphingosine levels in Gaucher disease [23].

Dried blood spots and alternative sample mediums

The collection and processing of invasive biofluid samples (e.g. plasma) are prone to difficulties, with many assays requiring specific processing and storage protocols to limit sample degradation [24]. Consequently, the exploration of potentially minimal or non-invasive sample collection techniques seeks to facilitate the ease, time, cost and stability of bio-sampling. This section presents five original research articles that are focused on the use of alternative sampling approaches. The first two papers apply the use of dried blood spots (DBS) for potential application to newborn screening [25] and routine vitamin D assessments [26]. The third presents analyses using volumetric absorptive microsampling (VAMS), an alternative approach to DBS [27]. The next article considers the clinical application of Paper Spray-MS [28], and finally we offer an intriguing use of nasal exudate for the classification of stroke [29].

This finalizes Part I of this special issue dedicated to MS in the clinical laboratory. Please return for Part II in the next issue where topics will cover *quantitative protein assessment*, *MALDI-MS for the clinic*, *clinical application of 'omics technologies* and *laboratory automation and kit-based approaches*.

On behalf of the *Clinical Chemistry and Laboratory Medicine* editorial team, I would like to express my gratitude to the authors who submitted their work for consideration and the reviewers who provided their time and effort to ensure the quality of these publications. I sincerely hope you enjoy reading the excellent work presented in this special issue as we look forward with excitement to the coming years and continuing journey of MS within the clinical laboratory.

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