Liquid Chromatography–Mass Spectrometry Education for Clinical Laboratory Scientists

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KEYWORDS

• Liquid-chromatography–tandem mass spectrometry • Training • Competency

KEY POINTS

- Quantitative liquid chromatography–tandem mass spectrometry (LC-MS/MS) as used in diagnostic laboratories is highly complex and requires a theoretic knowledge base and hands-on expertise by bench technologists, managers, and directors to insure acceptable quality and productivity.
- Training for quantitative LC-MS/MS is not included or is covered only briefly in programs for clinical laboratory scientists and may or may not be addressed in clinical chemistry fellowship and pathology residency training programs. As a consequence, training for this subspecialty takes place primarily on the job, within the diagnostic laboratories performing the testing.
- This article stratifies and lists the competencies required for bench personnel, research and development scientists who develop and validate methods, laboratory managers, and directors as an aid toward designing training curricula and assessing trainees and staff.

INTRODUCTION AND BACKGROUND

The world of quantitative diagnostic mass spectrometry (MS) is evolving toward automation and greater ease of use. For diagnostic laboratories, that means migration from manual procedures in esoteric testing sections of the laboratory to automated,

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high-throughput core laboratory sections. The holy grail of diagnostic MS automation is regulatory-compliant quantitative assays (eg, Food and Drug Administration approved or Conformité Européene [CE] mark) on a fully automated liquid chromatography (LC)–tandem mass spectrometry (MS/MS) instrument. Such a system would have ease of use similar to automated clinical chemistry analyzers—random-access workflow, minimal down-time, 24/7 service and support, and validated and ready-to-use reagents and calibrators supplied by the vendor. These systems would not require specialized end-user skills for operation and would have sampling and software that permit integration to track systems along with ASTM/HL7 interfaces to laboratory information systems.

A parallel goal is that no trade-off will have been made between ease of use and the impressive sensitivity, selectivity, and precision that are possible with LC-MS/MS. At this time, at least 1 vendor has made significant progress toward these goals and is poised to ship quantitative LC-MS/MS instruments designed for operation in highly automated diagnostic core laboratories.

To clarify terms, this article uses *diagnostic laboratory* to define settings in which the sole purpose of laboratory testing is to report results to the medical record for patient care in a regulated environment. Because MS is widely used in clinical research and clinical trials as well as diagnostic laboratories, *clinical MS* is defined as the much broader and less regulated practice encompassing all those activities, of which *diagnostic laboratory MS* is a smaller subset.

Why has quantitative LC-MS/MS remained, until now, a specialized practice, widely used in commercial diagnostic reference laboratories but not feasible in many hospital laboratories? Primary barriers for hospital laboratories are the expertise required to develop and validate procedures[1,2] and the challenging finances associated with large capital expenses for initial instrument purchases. In stark contrast, use of qualitative MS in the diagnostic microbiology laboratory has been rapidly adopted by most hospitals, transforming routine practice. The value proposition of matrix-assisted laser desorption/ionization (MALDI)-time of flight (TOF) in the microbiology laboratory is well justified based on reduced time to identification and decrease in reagent costs.[3,4] Because qualitative MALDI-TOF MS for diagnostic microbiology is becoming the norm, the technique is being integrated into training programs at all levels. The other rapidly developing field in diagnostic MS is imaging. The differences between training for imaging MS versus for quantitative LC-MS/MS are profound. Avoiding detail to address the 2 subspecialties in 1 article does both a disservice. Therefore, this article selectively addresses training for quantitative diagnostic LC-MS/MS, only 1 of the areas in which MS has become important in laboratory medicine.

If automated LC-MS/MS is widely implemented in core laboratories, then basic LC and MS/MS theory will become a standard feature in training curricula, as for spectrophotometry and electrophoresis. Will the need for personnel in diagnostic laboratories with specialized hands-on LC-MS/MS training disappear? An analogy can be made to typesetting—once a highly skilled, multifunctional profession that was made obsolete by revolutions in printing technology.[5] The premise of this article is that routine production with quantitative laboratory developed tests (LDTs) using stand-alone, open LC-MS/MS instruments will remain financially viable for some time in diagnostic laboratories. Therefore, the extensive training needed for such practice is described in detail.

Diagnostic laboratories that perform quantitative LC-MS/MS testing now have tremendous variance in their extent of automation, throughput, and test workload. The authors believe more useful descriptors than these to distinguish between current versus new MS testing paradigms are the site of assay development/validation and whether the LC-MS/MS system is open or closed. Open instruments can be used