Q&A

With **Professor Brian Keevil**
Consultant Clinical Scientist and Head of the Clinical Biochemistry Department at the University Hospital of South Manchester

Standardizing LC-MS/MS

The good, the bad, and the future of clinical diagnostics

LC-MS/MS is fast emerging as a powerful analytical tool with an already wide, and growing, range of applications in diagnostic testing. We spoke to Professor Brian Keevil, a Consultant Clinical Scientist and Head of the Clinical Biochemistry Department at the University Hospital of South Manchester, to get his expert opinion on the importance of LC-MS/MS standardization in the clinical laboratory, and how a new dedicated LC-MS/MS system could help to resolve the many challenges of standardization.

Background

As the technology underpinning clinical LC-MS/MS analyzers has advanced over the last 10 years, LC-MS/MS has established itself as an important analytical tool, and the number of potential applications for its use in diagnostic testing has exploded. In addition, due to its high specificity, LC-MS/MS will probably supersede alternative analytical tools, such as immunoassay-based methods, which suffer from interference and can give unreliable results. As such, LC-MS/MS offers the chance to transform our ability to diagnose and, therefore, treat many diseases, including those that are life-threatening.

Despite its great potential, LC-MS/MS is still not being adopted by laboratories as quickly or as widely as expected. Current LC-MS/MS systems involve multiple complex, manual stages, and in order to use the technique to its full potential, laboratory staff may require specialist training. In addition, the lack of standardization of LC-MS/MS methods is deterring clinical laboratories from using them.

In an in-depth Q&A with Professor Keevil, we try to get to the bottom of why proper standardization of LC-MS/MS methods has been so difficult, why it is important, and how it could be achieved in the future.

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About Professor Brian Keevil

Professor Keevil is an internationally recognized expert in the use of LC-MS/MS in the clinical laboratory. He has a special interest in LC-MS/MS methodology, and has developed many techniques for its routine and research use, particularly for therapeutic drug and steroid monitoring.

Talking about the importance of LC-MS/MS, Professor Keevil says: “Up until about 10 years ago, LC-MS/MS systems were perceived as just another ‘toy’ to have a play on occasionally – but now people are finding a growing number of routine applications for it. LC-MS/MS is now recognized by the research community as the gold standard, so researchers and laboratories need to use it to perform viable research programs and to get their work published.”

Professor Keevil’s laboratory is equipped with multiple LC-MS/MS systems to perform all the routine tests for the University Hospital of South Manchester (UHSM) NHS Foundation Trust, a major acute teaching hospital trust in the UK. As well as the routine tests for UHSM, Professor Keevil’s laboratory also takes referrals from other laboratories and performs tests that others are not equipped to do themselves. The team also undertakes research and assay development.

As an important LC-MS/MS hub of diagnostic testing and research, standardization is hugely important to Professor Keevil’s laboratory. “Standardization is necessary to ensure we obtain the correct results, and that they agree with the results of other laboratories, particularly in therapeutic drug monitoring and endocrinology applications,” Professor Keevil says.

However, a number of issues have barred the way to achieving appropriate LC-MS/MS standardization, so we were curious to find out why Professor Keevil thinks it has been so unattainable.

Q&A

Q: Why is standardization challenging?
A: “One barrier to laboratories using LC-MS/MS has been the issue of properly standardizing LC-MS/MS methods. This challenge arises because different laboratories use a wide range of techniques and equipment; for example, ionization probes/procedures, collision gases, sample clean-up procedures, chromatography columns, calibrators, and internal standards can all differ among laboratories and offer different results.

All this variation means that it’s very difficult to achieve proper standardization of LC-MS/MS results. This is particularly relevant for certain specialties, such as endocrinology, where clinicians have been acutely aware of the problems for a long time.”

We went on to ask Professor Keevil about the kind of impact a lack of standardization could have when using LC-MS/MS for diagnostic testing.

Q: What makes standardization crucial?
A: “A lack of standardization is problematic for two main reasons. Firstly, it becomes very difficult to control one’s own laboratory results, because without standardization they could change from year to year. Secondly, a lack of standardization can create discrepancies between different laboratories; two laboratories performing the same measurement could get different results.

A further challenge is the need for each laboratory to have its own reference ranges developed in-house. These are difficult to develop for numerous reasons, including the need to obtain ethical consent, generate financial investment and find a normal reference population. It would therefore be much more beneficial to standardize methods among laboratories using one common set of reference values.

Of course, the implications on patient care are also significant, as a lack of standardization could lead to the wrong diagnosis and, ultimately, the wrong treatment.”

As a lack of standardization threatens the continuing adoption of powerful LC-MS/MS analytical techniques, and could potentially have serious consequences on patient care, we wanted to hear Professor Keevil’s ideas on how to address the issue.

Q: So, is there a solution?
A: "Standard LC-MS/MS systems were designed for the research laboratory, so they are ultra-configurable and great for developing methods. However, what the clinical laboratory needs is a dedicated system that not only promotes, but also facilitates standardization; and the lack of such a system has presented a significant barrier to uptake so far.

Studies have shown that by carefully using the same instrument, column, protocol, and methods, it is in fact possible to generate consistent results from LC-MS/MS systems at different laboratories – so we know it can be done. A dedicated system with standardized procedures, which are used by every laboratory would make this much easier.

Such a system would be optimized for the specific methods laboratories want to run. In particular, columns, reagents, calibrators and controls would all need to be known and dedicated to that system, and this should be consistent. Also, the data generated must be reproducible and accurate. Finally, a dedicated clinical LC-MS/MS system must be automated and easy to use, which I think is hugely important for the clinical laboratory. It needs to be usable by anyone, even the most junior, inexperienced staff, so they can simply load samples and walk away."

The dedicated system that Professor Keevil has in mind would be crucial to standardizing LC-MS/MS methods in clinical diagnostics, and would help to ensure patients were properly diagnosed and treated. However, we were interested to find out whether a dedicated system would really work in practice, and what the broader implications would be if it was to become available.

Q: Would a dedicated system be a game-changer?
A: "If a network of laboratories was to start using such a dedicated clinical LC-MS/MS analyzer, they would be able to adopt common reference ranges and reagents, providing much greater confidence in the consistency of results.

For example, if a patient was transferred to a different hospital, you could be confident that the test results would be the same at each and, therefore, directly comparable, as long as both laboratories were using the same system.

There is currently a big drive from organizations, such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the Centers for Disease Control and Prevention (CDC) and the Endocrine Society, towards harmonizing assays among laboratories and improving quality levels. So, the adoption of a single dedicated system among a laboratory network would certainly help.

I think a dedicated clinical LC-MS/MS would prove useful in larger laboratories, particularly those without LC-MS/MS experience, if you could just plug it in, press a button, and walk away. Although, I'm sure laboratories with LC-MS/MS experience would use it too.

Laboratories without LC-MS/MS experience could immediately start using a plug-and-play LC-MS/MS in place of immunoassay-based tests, which could help to generate much higher quality results, particularly for steroid work."

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Conclusion

Drawing on Professor Keevil's many years of experience of using LC-MS/MS in his busy clinical laboratory offers a valuable perspective on just how important, yet challenging, proper standardization is in keeping this technology at the top of its game.

For Professor Keevil, an automated, dedicated LC-MS/MS system would enable inter-laboratory standardization. Interference-prone immunoassay-based tests could be phased out and replaced by clinical LC-MS/MS analyzers; and there would be no doubt in anyone's mind that the results obtained from one laboratory would be consistent over the years and also match those results generated by other laboratories using the same system.

Importantly, a dedicated clinical LC-MS/MS system could be used by the whole laboratory team, including junior and untrained members. Staff would no longer need in-depth, specialist training for routine work and consequently, laboratories would see decreased training costs, increased flexibility, and even the opportunity for more experienced staff to undertake cutting-edge research and development.

Furthermore, the research community's confidence in the reliability of LC-MS/MS could skyrocket, fostering the generation and proliferation of future research programs and potential breakthrough discoveries. Ultimately, this could lead to ensuring patients are receiving the most accurate test results possible to facilitate accurate disease diagnosis and treatment.

Thermo Fisher Scientific has listened to customers and is addressing the needs of clinical laboratories through the Thermo Scientific™ Cascadion™ SM Clinical Analyzer. This dedicated clinical LC-MS/MS analyzer is accurate, easy-to-use and designed for the clinical laboratory. As a fully integrated system, the Cascadion analyzer allows clinical laboratories to fully leverage the power of LC-MS/MS technology.

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