that ctDNA is measurable for a variety of advanced cancers.

Much like other serum cancer markers, ctDNA can detect residual tumor noninvasively. However, studies demonstrate superior diagnostic sensitivity of ctDNA over both protein biomarkers and circulating tumor cells for therapeutic monitoring. Moreover, by interrogating established resistance mechanisms, ctDNA may reveal impending expansion of low-abundance resistant clones earlier than current monitoring protocols. One example of this possibility is work showing the emergence of \textit{KRAS} (kirsten rat sarcoma viral oncogene homolog) mutations in EGFR (epidermal growth factor receptor) inhibitor–treated patients on average 5 months before demonstration of tumor progression by surveillance imaging (3). However, this targeted approach is not universally applicable because it may overlook other equally relevant alterations. Researchers have detailed tumor heterogeneity and discovered unique paths to therapeutic resistance by the unbiased method of whole exome sequencing. Today, however, this approach is far too costly to be performed clinically. A proposed middle ground includes focusing on the portion of the genome most commonly mutated in specific cancers, an approach that, in theory, could minimize missed mutations while moderating costs.

Despite its impressive analytical sensitivity, ctDNA analysis currently remains insufficient at early detection of tumors. Some argue that further advances in technology will overcome this obstacle and make ctDNA a viable screening method. However, as with many ultrasensitive clinical methods, increased sensitivity carries with it new challenges in interpreting the clinical significance of the results. Do rare mutations in circulating DNA necessitate extensive workup for an occult malignancy? Do such abnormalities even possess malignant potential? Is ctDNA even truly representative of the tumor from which it comes? Despite the wealth of information this technology provides, the critical question remains as to how it can best direct clinical action to improve patient outcomes. Longitudinal studies are ongoing, pairing tissue biopsy with ctDNA “liquid biopsy” to address some of these questions.

As ctDNA technology pushes the boundaries of cancer detection, it has outdistanced the current armamentarium against cancer. A mutation driving resistance may be found, yet no therapy to target this aberrant pathway may exist. Still, although ctDNA may uncover as many undruggable as actionable mutations, its utility as a research tool is undeniable. And pharmacologic science may eventually catch up to our ability to understand cancer evolution by advanced genetic techniques like ctDNA analysis. As such, it may yet prove to be a critical component of realizing the ultimate goal of personalized medicine in oncology.

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References


Recommended Reading for Rookie LC-MS Users

The love affair between laboratory medicine and LC-MS is showing little sign of waning. Clinical chemists have enthusiastically embraced LC-MS due to its often superior analytical performance and high-throughput capabilities. However, for clinical LC-MS users, the unique set of challenges with developing and implementing robust LC-MS methods...
for routine clinical use cannot be understated. For this rea-
son, and the fact that the clinical LC-MS market is under-
going significant growth, manufacturers have responded by
placing greater emphasis on providing specific LC-MS so-
lutions for clinical applications. However, despite attempts
to move clinical LC-MS into the so-called “black box” cate-
gory of methods, there are still many potential pitfalls for the
nonspecialist. In many cases, laboratories acquire LC-
MS systems having given little consideration as to their prac-
tical implementation, particularly in the absence of prior
LC-MS experience. In 2013, the Royal Society for Chem-
istry Analytical Methods Committee produced a guide that
encompasses the main practical considerations in the devel-
opment and validation of quantitative LC-MS assays (1).
This document is one of the most comprehensive and com-
plete resources available for new LC-MS users. The authors
have managed to successfully cover all of the most important
aspects one should consider when approaching LC-MS,
from selection of sample clean-up procedures to reporting of
results. This document should be at the top of the recom-
mended reading list for anyone tasked with implementing a
clinical LC-MS assay.

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Reference

1. Sargent M, ed. Guide to achieving reliable quantitative LC-MS measurements: RSC
Analytical Methods Committee. 2013. www.rsc.org/images/AMC%20LCMS%