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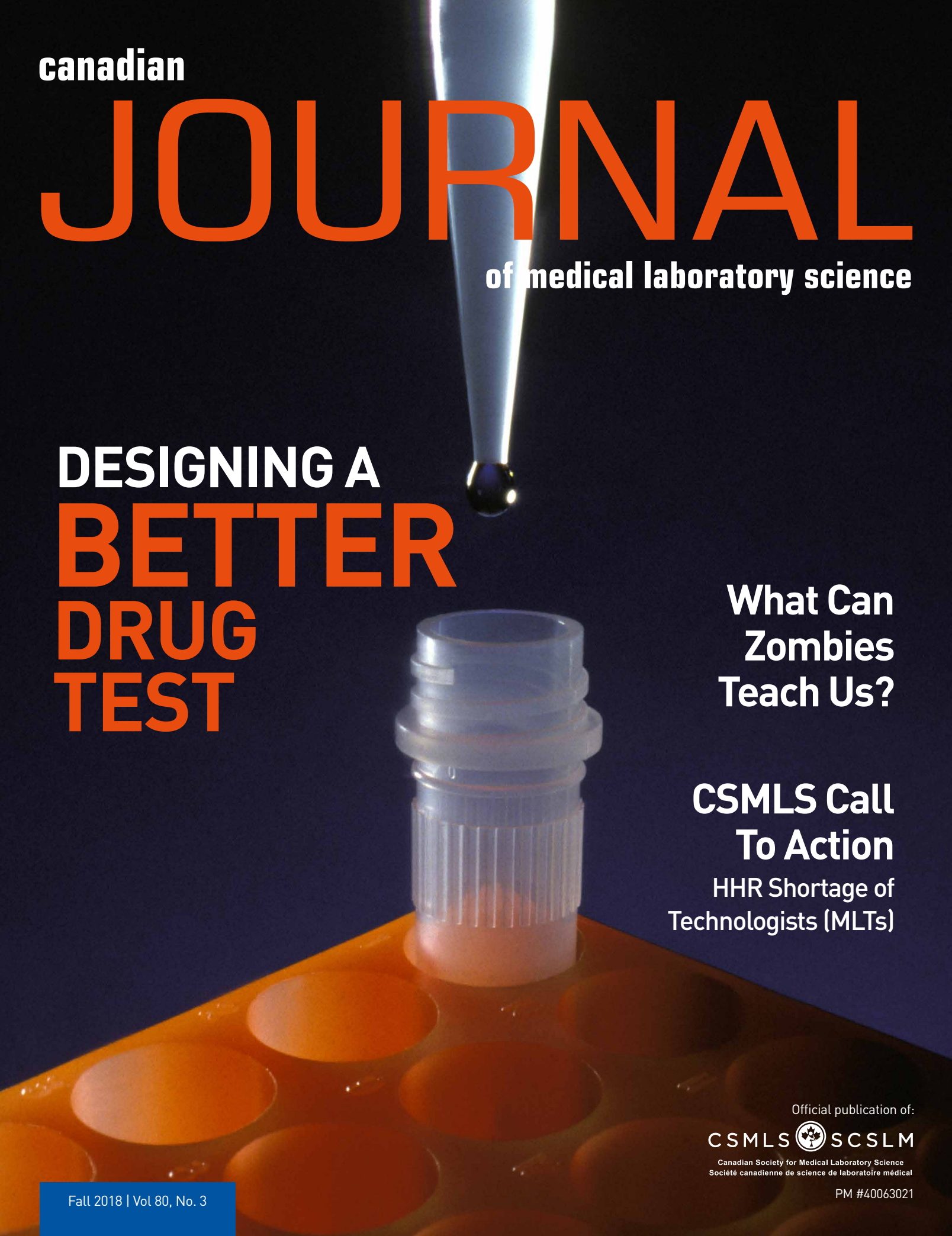

DESIGNING A BETTER DRUG TEST

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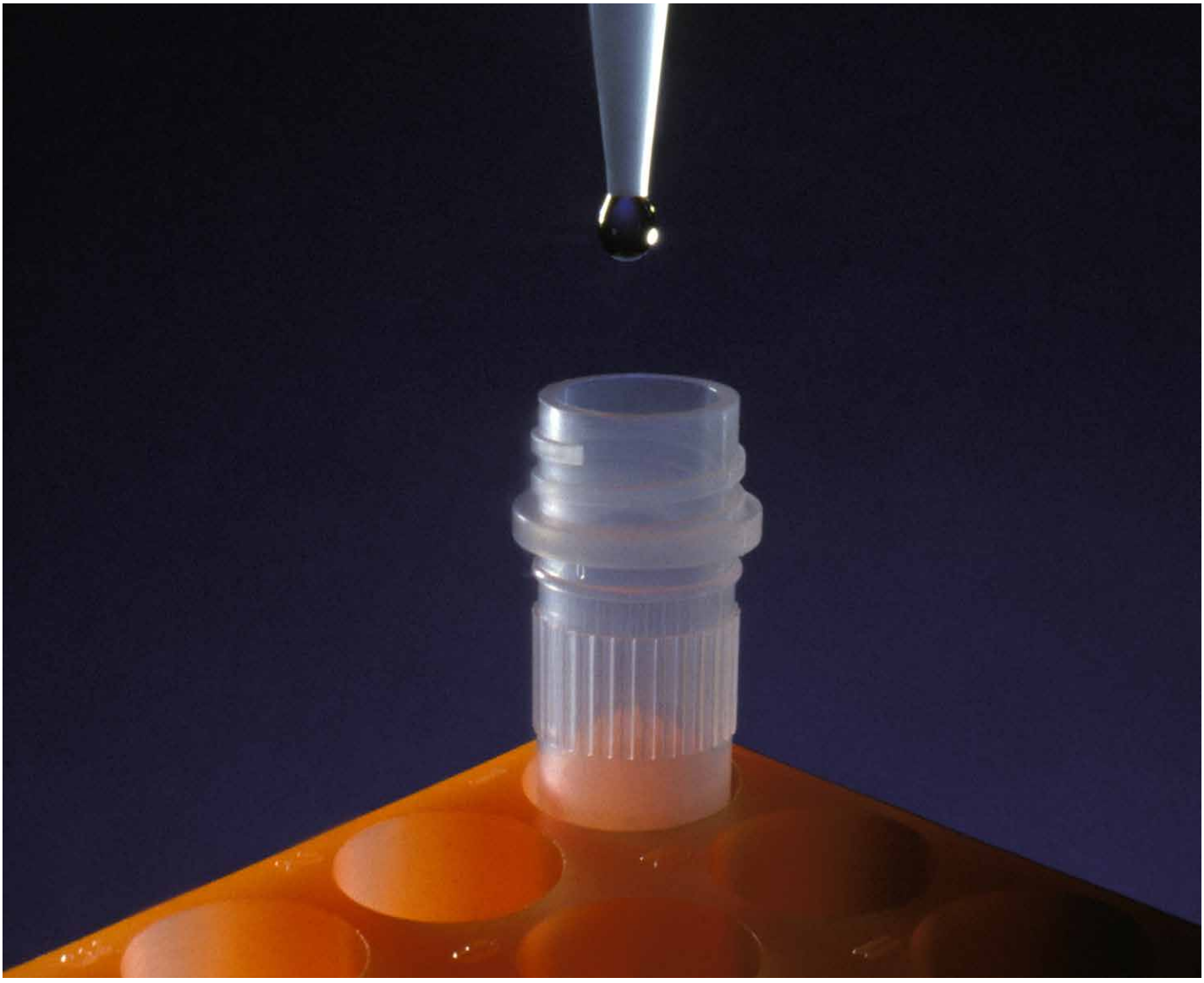

Designing a Better Drug Test

"As deaths and hospitalizations due to opioid abuse continue to rise, a highly accurate, faster and more cost-effective drug screening methodology is in development." »

Kristin Hauff, PhD, FCACB, a clinical biochemist at the Kelowna General Hospital, oversees chemistry for the Interior Health Authority in British Columbia, a network of 31 lab facilities within hospitals and community health centres serving a broad geographic footprint in the province. She has seen a marked increase in the volume of drug tests over the last several years due to the opioid crisis, especially after the British Columbia Ministry of Health mandated regular drug screening for patients taking prescribed opioids.

What Hauff has witnessed at Interior Health is just one example of the opioid crisis that has gripped many communities in Canada and continues to put increasing pressure on medical labs. Canada is the second largest consumer of prescription opioids per capita in the world after the United States.[1] In 2017, about 4,000 Canadians died from an apparent opioid-related overdose, up from almost 3,000 in 2016, while 29 per cent of Canadian adults reported using some form of opioid in the past five years.[2] The western provinces have been hit the hardest and the trends have generally spread across the country. The Canadian Institute for Health Information estimates that 29.3 people in British Columbia were hospitalized every day in 2017 due to opioid poisoning, an increase of about five per cent over 2016 and well above the Canadian average of 16.4 people.[3]

Current drug testing involves a two-tiered approach that starts with immunoassays, which use automated analyzers to detect the presence of drugs using antibodies, followed by mass spectrometry to confirm and identify known drugs and their metabolites. Immunoassays are fast and easy, but they can only identify substances that resemble target drugs. Moreover, the antibodies used in these immunoassays are only available for commonly known drug classes and take years to develop.

"For opioids, immunoassays look for morphine and two other opiates that look like morphine – codeine and heroin. Doctors are hoping to see oxycodone, fentanyl and other opioids that are out there, but immunoassay is blind to those," explains Hauff. "In the current environment, we're really struggling with the fact that immunoassays are not adaptive. With all of the different analogues and synthetic drugs coming out of basement chemistry labs, as soon as we develop a test to identify them, people have moved on to something different." Immunoassays are also prone to false positives due to antibody cross-reactivity for commonly prescribed opioids, illicit drugs and certain foods, and they also have high false negatives for certain drug classes like benzodiazepines.

Mass spectrometry – historically gas chromatography-mass spectrometry and increasingly liquid chromatography-tandem mass spectrometry – is considered the gold standard test because it is highly accurate and very specific. However, it requires expensive equipment, specialized training and more processing time compared to immunoassay. Interior Health does not have mass spectrometers at any lab sites, so they send samples for testing to health authorities in the Lower Mainland. Depending on the test, the turnaround times range from 72 hours to two weeks.

A new invention currently in development may provide a faster, more accurate and cost-effective test for drug screening in the future. Philip Britz-McKibbin, PhD, a professor in the Department of Chemistry and Chemical Biology at McMaster University in Hamilton, Ontario, has developed a novel drug testing methodology that can identify more than 50 specific drugs and their metabolites in a fraction of the time, as compared to the current two-tiered approach. The methodology is called multisegment injection-capillary electrophoresis-mass spectrometry (MSI-CE-MS). It couples high-efficiency electrophoretic separations to high-resolution mass spectrometry with full-scan data acquisition, enabling non-targeted screening of large numbers of drugs and their metabolites in human urine. This multiplexed platform analyzes 10 or more samples simultaneously, bringing the run time to under three minutes

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per sample with better accuracy, selectivity and coverage than conventional immunoassays.[4] Britz-McKibbin explains, "The first sample of the serial injection analyzed is an expanded drug panel mixture at the cut-off level. Each run after that contains randomized urine samples from individual patients that we compare directly with the first injection as the reference."

For more than 14 years Britz-McKibbin's group at McMaster University has been focused on developing new tools for clinically-based metabolomic studies, the comprehensive analysis of small molecules in biological fluids, as a way to discover new biomarkers for early detection of treatable diseases. He patented the MSI-CE-MS methodology in 2016.[5] To test the concept, he collaborated with Howard Lee, CEO of Seroclinix Corporation, a clinical and animal diagnostic lab services organization, and Marcus Kim, a mass spectrometry specialist at Agilent Technologies, a laboratory solutions company. Both organizations are based in Mississauga, Ontario. "We immediately recognized the value of the new methodology. The ability to do multisegment analysis to reduce time and cost is a tremendous benefit," says Lee.

In a proof-of-concept study using 117 de-identified urine samples, the collaborators are planning to demonstrate that the MSI-CE-MS can accurately detect and rapidly identify over 50 drugs of abuse at the recommended screening cut-off levels. Britz-McKibbin says, "The methodology is very specific: identification is confirmed by matching an illicit or prescribed drug's accurate mass or molecular formula together with its migration time for cases with concentrations measured above the cut-off level, including the detection of related drug

29%

of Canadian adults reported using some form of opioid in the past five years.

metabolites in urine. As a result, the chances for false positives are extremely small."

Among the drugs that can be detected are specific opioids, including oxycodone, tramadol, methadone and norfentanyl, as well as a wide range of benzodiazepines, antidepressants, stimulants and sedatives. The MSI-CE-MS does not detect synthetic cannabinoids or barbiturates since they are acidic drugs and therefore poorly ionizable in positive ion mode testing. However, Britz-McKibbin says that changing the mode to negative ion detection with alkaline buffer conditions for separation is currently under development. In their published paper, the researchers also note that the innovation can be used retrospectively to identify drug metabolites or emerging classes of synthetic opioids in situations where antibody reagents or reference standards do not exist.[4]

As luck would have it, one day at a clinical research symposium, Britz-McKibbin met Dr. Zainab Samaan, a psychiatrist at McMaster University, who oversees the Mood Disorders Program at St. Joseph's Healthcare Hamilton. As the only chemists in the crowd, they discovered their shared interest in metabolomics and a connection between their two disciplines. Together with Lee and Kim, they collaborated and conducted a pilot study to test the MSI-CE-MS using 220 de-identified and blinded urine samples from patients in the Mood Disorders Program.

Patients in this group take well over 150 different medications and a large number of them take multiple psychoactive medications, including prescribed opioids, antidepressants and antipsychotics. Therefore, the urine samples provided a robust challenge to determine whether the MSI-CE-MS could accurately identify drugs compared to the patients' medical records. The investigators also compared the new methodology with the standard two-tiered approach over a three-week period. Full results from the pilot study will be published soon, but Britz-McKibbin says, "The most surprising result with our untargeted method was the sheer number of non-prescribed drugs that were not indicated in the medical record."

Determining exactly what patients are taking is essential information for physicians. Accuracy is paramount to confirm adherence to prescribed medications and to identify undisclosed substances patients are using to self-medicate. Undisclosed substances may decrease the effectiveness of prescribed drugs or increase the risk of dangerous drug interactions. The MSI-CE-MS platform is untargeted and adaptive, meaning that it can screen for a virtually unlimited number of drugs provided they can be both resolved and detected. "The data can inform us if a designer drug is present. That's a big advantage over immunoassay alone which can only bind to a known class of drug and does not distinguish between single or multiple drugs of the same class," says Britz-McKibbin. "Our invention can also determine whether a urine sample is real or synthetic. On the Internet, people can purchase synthetic urine that is negative for any drug and passes routine specimen verification tests performed at most labs. We hope our invention will put the synthetic urine industry, that's been designed to evade drug testing and has direct impacts on human health, out of business."

At Interior Health, Hauff says that an important part of her role is educating doctors to ensure that they are using current drug screening tests appropriately. "Sometimes, they expect to see a drug, but when it doesn't turn up in the test, they automatically assume that the patient did something nefarious, like diverting their prescription. The truth is that the testing was not appropriate for the drug that they were looking for," Hauff says. One aspect of the pilot study for the MSI-CE-MS was to validate a proprietary software system developed by Seroclinix. The "middleware" analyzes the data, interprets it and provides physicians with actionable reports that include drug names, cut-off levels, indications of patient adherence, the names of any non-prescribed medications and guidance on potential drug interactions or adverse effects.

For the next step in the development process, this fall Britz-McKibbin, Lee and Kim are conducting a live beta test of the MSI-CE-MS in three labs owned by Seroclinix, the exclusive patent licensee. The Clinical Laboratory Improvement Amendments (CLIA)-accredited labs

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>
> Philip Britz-McKibbin, professor, Department of Chemistry and Chemical Biology, McMaster University

are located in Buffalo, New York; Dallas, Texas; and Raleigh, North Carolina. "We are very interested in commercializing this new technology. Our plan is to beta test and launch in the United States first and then extend to other countries," says Lee.

Britz-McKibbin adds, "In the United States, there are many more labs per capita, many people take multiple medications, yet current methods test for single drugs at a time, so costs are out of control. Insurance providers are looking for ways to reduce costs."

Lee adds, "This is an exciting technology that would be beneficial in this country, too. Lowering costs would also fit in well with the more socialized approach to medicine in Canada."

If the MSI-CE-MS is commercialized successfully in the United States, the collaborators plan to expand it to Canada in the future. In the meantime, Hauff is looking to bring mass spectrometry to Interior Health within the next year or so. "The chances of us getting a mass spectrometer in every site is impossible and moreover, that's not ideal. The optimal drug testing strategy will continue to be a combination of immunoassay and mass spectrometry because there's currently no single method that can deliver on all four parameters of timeliness, accuracy, cost-effectiveness and adaptability," Hauff says. "But even if I can't deliver a mass spectrometer at every site, we would still be able to provide results before a patient is treated and goes home. The information won't be as timely, but it will still be useful for monitoring patients on a population scale."

She envisions a future where labs will aggregate population data on highly potent drugs, such as the fentanyl analogues that are currently behind a large majority of overdose deaths occurring in British Columbia and across Canada. In 2016, for example, 68 per cent of the 985 deaths due to illicit drugs in British Columbia involved fentanyl.[1] "It's not the polypharmacy from the doctors so much as the polypharmacy from the street. People are unknowingly getting highly potent fentanyl while thinking that they are taking another

drug, like cocaine or methamphetamine," says Hauff. "Sharing information among toxicology labs across Canada is starting to occur and will help us all become more adaptable to the newest drugs we need to detect and monitor so we can help more physicians improve patient outcomes."

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