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Urine Drug Testing in the Era of Opioid Crisis

Chronic pain management with long-term opioid therapy, typically involves prescribing potentially addictive substances. In patients taking other nonprescription medications or illicit drugs, this affords an additional risk of fatal drug-drug interactions. Over the last decade drug overdose deaths, including those involving opioid have increased six times and surpassed deaths from guns, HIV, and car crashes. Consequently, in 2017, the U.S. Department of Health and Human Services declared the opioid crisis, a public health emergency. Although prescription rates have decreased in response to the crisis, the average days of prescription supply have increased and approximately 40% of patients report inadequate pain management. It has become challenging for clinicians to provide necessary pain control while maintaining low risk for substance abuse.

A number of clinical tools for behavior-based risk assessment in addition to prescription monitoring programs to identify patients who are potentially administered controlled substances from multiple providers, are available for pain management programs. These clinical tools however rely on self-reporting and subjective interpretation of behavior, and

can prove unreliable. In contrast, laboratory testing provides an objective assessment of drug exposure and can substantially supplement existing clinical tools. Various professional societies/organizations and regulatory bodies in general agree that for a successful pain management program, urine drug testing (UDT) is an effective tool. UDT is recommended before the initiation of treatment with opioids and during therapy, not only to assess compliance but also to detect undisclosed substances and diversion. Consequently, UDT test menu offered must include both commonly prescribed medications as well as commonly abused drugs.

UDT for pain management has followed a forensic model, which is primarily based on Department of Human and Health Services guidelines and protocols for drug of abuse testing. As such, immunoassays are typically used as first-line screening test. Immunoassays offer several advantages including ease of use, fast turn-around-time, non-invasive collection, and lower cost. The main disadvantage of immunoassays is false-positive and false-negative results. In forensic model, positive immunoassay is followed by a definite or confirmatory test such as mass spectrophotometry to avoid false-positive results. With this approach, however false-negative results remain a problem. Furthermore, the Federal Drug Administration approved immunoassays commonly use higher cut-off concentrations, originally designated by Federal Workplace Drug Testing Programs mandated guidelines. These standard cut-off concentrations, developed by the Substance Abuse and Mental Health

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Services Administration (SAMHSA) of the US government were not established with pain-management or long term opioid therapy (in mind).

Currently, there is insufficient evidence in the literature for determination of standard cut-off concentrations or limit of quantification to effectively determine full compliance, partial compliance, and/or misuse/abuse of controlled drugs by pain management patients. Most non-reference or community based laboratories depend on manufacturers cut-off for the immunoassay used. At Saint Luke's Hospital, the in-house urine drug screen test performed uses manufacturer's standard cut-off concentrations and is specifically suitable in urgent clinical scenarios such as emergency and inpatient population. Use of this test in the out-patient setting has resulted in false negative results. To address this issue, we are working in collaboration with LabCorp to roll out a comprehensive urine drug screen testing for primary care clinics managing patients with prescribed pain medication. Meanwhile, the test is being built in EPIC, Saint Luke's Hospital is working with Opioid Stewardship Committee to provide appropriate UDT for primary care clinics.

Human Herpesvirus-6

There are eight human herpesviruses (HHV), including herpes simplex (HSV), varicella zoster (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesviruses-6, 7, & 8. All are double-stranded DNA enveloped viruses and are further subgrouped, based on biologic behavior, into alpha herpesviruses (HSV-1, 2, and VZV), beta herpesviruses (HHV-6, HHV-7, and CMV) and gamma herpesviruses (EBV and HHV-8).

A common characteristic of HHV's is the establishment of latency following primary infections, with potential for subsequent reactivation. Primary infections are common in normal hosts, with nearly all adults having been infected HSV-1, VZV, EBV, HHV-6 and HHV-7. Alpha herpesviruses characteristically cause mucocutaneous infections in otherwise healthy individuals and become latent in sensory neuroganglia. Beta herpesvirus infections become latent in mononuclear cells, while gamma herpesviruses are latent in lymphoid cells. Asymptomatic shedding of virus from oral mucosa is a characteristic of HSV, EBV, CMV, HHV-6, and HHV-7, and frequently results in person-to-person transmission. In contrast, VZV is transmitted only during primary infection (chickenpox) or reactivation (shingles) and is the only herpesvirus spread through airborne transmission. Reactivation of herpesviruses is most common in, but not limited to, immunocompromised individuals with impaired T-cell immunity. Both EBV and HHV-8 have associated malignancies, including lymphomas (EBV & HHV-8) and Kaposi's sarcoma (HHV-8).

Reactivation and shedding of herpesviruses has been studied in astronauts during shuttle missions and International Space Station flights. Increased levels of stress hormones coupled with immune system dysregulation results in the majority of astronauts from both settings (53% and 61%, respectively) shedding one or more HHV's in tested urine and saliva samples. The majority of astronauts are asymptomatic, however live virus has been recovered from skin lesions during and post-flight. (Rooney, et al, Front. Microbiol. 10.16; Feb 2019). HHV-6 was initially recognized in patients with

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lymphoproliferative disorders. Most HHV-6 primary infections occur by age three, and in immunocompetent children presents as roseola infantum or sixth disease. Primary infections in adults are rare, and not associated with specific symptoms. The majority of HHV-6 disease in adults is due to reactivation of latent virus in immunocompromised individuals. Transplant patients, particularly those with hematopoietic stem cell transplants (HSCT) are most at risk. Clinical HHV-6 disease in transplant patients include pneumonitis, hepatitis, encephalitis, and bone marrow suppression.

A unique property of HHV-6 is the potential for chromosomal integration of the virus into an individual's genome, which occurs in approximately 1% of the general population. This endogenous virus can be detected by serologic and molecular PCR testing. Coupled with the potential for virus shedding, positive diagnostic tests for HHV-6 can be challenging to interpret and the clinical context should always be taken into consideration. A recently published review of Filmarray meningitis panel results (Clinical Infectious Disease 2018;67(7):1125-8) summarized 15 patients whose CSF tested positive for HHV-6. Only one patient, who was an HSCT recipient 3 weeks prior to testing, was believed likely to have true HHV-6 encephalitis. The remaining positive results were concluded to be due to HHV-6 viral chromosomal integration or subclinical reactivation of latent virus, i.e. viral shedding.

Saint Luke's Microbiology has performed meningitis/encephalitis panel testing by Filmarray since March 2017. A review of 221 meningitis panel results from August 2018 through February 2019 showed 21 positive results, including 7 HHV-6, 4

Streptococcus pneumoniae, 4 HSV-2, 1 HSV-1, 3 Enterovirus, and 2 *Cryptococcus neoformans*. Effective immediately HHV-6 will no longer be resulted as part of the meningitis/encephalitis panel. HHV-6 testing for patients at high risk of infection is available through a reference laboratory, and includes both IgM and IgG antibodies and PCR assays that can be performed on blood or CSF.

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