Cost Advantage and Improved Accuracy of Medication Compliance by a Qualitative Time-of-Flight Mass Spectrometry and Immunoassay-based Screen in Pain Management and Drugs of Abuse Testing

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ABSTRACT Definitive quantitative methods, e.g. LC-MS/MS, are traditionally used in pain management (PM) and drugs of abuse (DOA) testing to confirm results from positive qualitative immunoassay screens. Novel strategies to screen urine without the need for subsequent confirmation, i.e. definitive screens, are of substantial clinical interest for the benefit of faster turn-around times, simultaneous parent compound and metabolite detection, as well as a broad analysis of drug abuse.

Qualitative, mass spectrometry-based methods can be used as definitive screens and can successfully identify individual compounds and metabolites within and between multiple drug classes. However, there may be instances when quantitation could provide additional clinical utility including the ability to distinguish drugs from pharmaceutical impurities, identify trends in the concentration of drugs with long half-lives in serial testing, and identify adulterated specimens. Further, quantitation and confirmation are often incorrectly tied together in the minds of ordering physicians and perpetuates the wide standing belief that quantitation is essential for urine drug compliance testing. In this study, compliance determination of 213 urine specimens analyzed by a comprehensive hybrid assay that combines heterogeneous immunoassays with acceptable performance and time-of-flight (TOF) mass spectrometry (hybrid screen) was compared to a conventional immunoassay screen with reflex to quantitative LC-MS/MS confirmation workflow (Fig. 1). Our objectives were to (1) assess overall compliance and frequency of polypharmacy or illicit drug use as determined by the conventional screen with reflex to quantitative confirmation versus TOF-MS-based qualitative analysis; (2) identify and determine the frequency of situations where quantitation provides additional clinical benefit; (3) evaluate performance of the current qualitative method with interpretation regarding compliance for the pain management setting; and (4) perform a cost analysis between a traditional screen to confirmation workflow to the hybrid screen workflow.

RESULTS The qualitative hybrid screen was superior to immunoassay screen alone or screen with reflex to quantitation in confirming compliance per prescription (226/302 vs. 198/302 vs. 205/302), as well as in identifying non-prescription substance abuse (97 vs. 67 vs. 71). While overall compliance and detection of substance abuse was superior in the hybrid screen, we identified 12 instances (3.8% of specimens) where quantitation was useful in distinguishing drug use from pharmaceutical impurities or to evaluate parent compound concentrations when metabolites were absent. Furthermore, our data set includes 26 specimens positive for THC and 12 positive for methadone (urine detection window 1-45 days and 1-14 days, respectively). Because of the prolonged urine detection of these compounds, quantitation could be beneficial in follow up testing with these patients when clinicians have advised cessation.

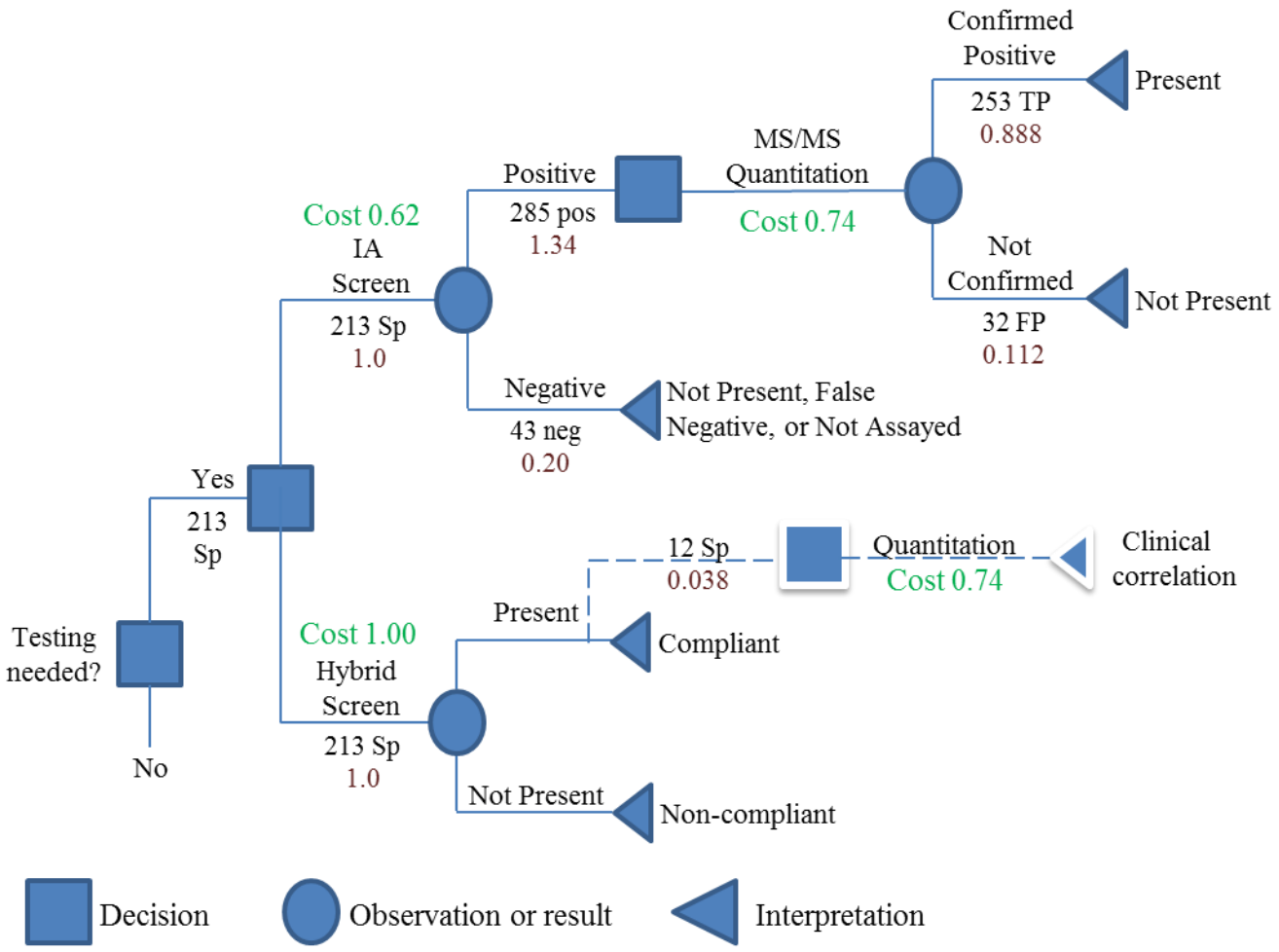
In assessing the false negative (FN) results of the hybrid assay, we found the majority were attributed to benzodiazepine detection. Because benzodiazepines are highly glucuronidated in urine, the hybrid screen, which measures non-glucuronidated (i.e. free) drug, has a sensitivity

disadvantage when compared to the quantitative LC-MS/MS workflow which includes enzymatic hydrolysis of glucuronidated metabolites (i.e. total drug). Many of these FNs are resolved in the data set by reporting to the limit of detection (LOD) instead of the established cutoff.

In performing a cost-analysis between the hybrid screen and the conventional screen to confirm workflow, we found a substantial cost benefit of 41% for the definitive hybrid screen (Fig. 1). On average, each specimen analyzed by IA screen is reflexed to confirmation at a rate of 1.34 confirmations per specimen with a false-positive rate of 11.2%. Conversely, reflex to quantitation post hybrid screen is useful at a rate of 0.04 per specimen, thus minimizing the expense of quantitative analysis.

CONCLUSIONS Definitive screens in pain management and drugs of abuse testing by qualitative mass spectrometry-based methods are an attempt to offer a less expensive, faster, and comprehensive evaluation of patient medication compliance and drug abuse. Our study of a hybrid definitive screening approach demonstrates increased accuracy of compliance and drug abuse determination, as well as a substantial cost benefit, when compared to a conventional immuno-based screen reflexed to quantitation. While drugs with extensive metabolism and glucuronidation are challenging to detect without hydrolysis, high-sensitivity qualitative MS screens have additional utility in reporting results to the LOD to mitigate reporting false negative results. Infrequently, subsequent quantitation may provide additional insight for interpretation of analyte ratios. Therefore, definitive screening approaches involving qualitative mass spectrometry-based methods are streamlined, cost-efficient, and effective in monitoring patient's drug compliance and drug abuse in a pain management setting.

Figure 1. Positivity and Cost Analysis. All testing costs are normalized to the average cost of the hybrid screen for clarity. Analysis of 213 specimens (Sp) by immunoassay (IA) screen (cost of 0.62/specimen) lead to 285 positive results (1.34/specimen) and subsequent confirmation by quantitation (cost of 0.74/confirm). Negative IA results (0.20/specimen) include false negatives, true negatives, and analytes that are not detected by the IA panel. Quantitation revealed an IA false positive (FP) rate of 0.112/specimen and a corresponding true positive (TP) rate of 0.888/specimen. The same specimens were tested by the hybrid screen and of the specimens with drugs present, a small subset (dashed line) could benefit from additional quantitation. Cost analysis between IA with confirmation (cost of 1.74/specimen) and hybrid screen (cost of 1.03/specimen), indicates a 41% cost savings in the hybrid screen workflow.



*All costs are normalized the average hybrid screen cost

IA to Confirmation Workflow
IA w/ Confirm (0.74*1.34) + (0.65*1.0) = 1.61
IA w/o Confirm (0.52*0.2) = 0.12
Total workflow = 1.74

TOF Hybrid Workflow
Total Worflow (1.0*1.0) + (0.74*0.04) = 1.03