precision diagnostics

nextgen precision testing

delivering unprecedented results

a white paper on evolving clinical drug testing cutoff levels to effectively identify drug abuse, misuse, and diversion

introduction

Prescription drug abuse, misuse, and diversion has increased significantly over the past two decades – along with the number of prescriptions for opioids and benzodiazepines. The use of clinical drug testing as a tool to address these issues has grown significantly as well, along with advancements in drug testing technologies. This white paper provides information on these trends.

financial costs of prescription drug misuse and diversion

Health economists from Johns Hopkins University writing in *The Journal of Pain* reported the annual cost of chronic pain is as high as $635 billion a year, which is more than the yearly costs for cancer, heart disease, and diabetes.[1] Total incremental costs of healthcare due to pain ranged from $261 to $300 billion, and the value of lost productivity ranged from $299 to $334 billion.[1]

The Coalition Against Insurance Fraud (CAIF), a national alliance of consumer groups, insurance companies, and government agencies, estimated that opioid analgesic abuse results in over $72 billion in medical costs each year.[2] Other, more conservative studies estimate the cost of opioid abuse to be $53-$56 billion annually, accounting for medical and substance abuse treatment costs, lost work productivity, and criminal justice costs.[3,4]

In a *Journal of Managed Care Pharmacy* study, patients "who were opioid abusers had health care costs that were more than eight times higher than those of non-abusers."[5] The total average per-patient direct health plan cost for opioid abusers was $15,884, compared with $1,830 for non-abusers, a difference of $14,054 per patient in 2003 dollars.[5] Assuming an average 3.5% annual increase in medical cost inflation, that difference would be $20,518 per patient in 2014 dollars.

Drug Overdose Deaths Involving Opioid Analgesics

In 2012, of the 41,502 drug overdose deaths in the United States, 22,114 (53%) were related to pharmaceuticals; 16,007 (72%) involved opioid analgesics.[5]

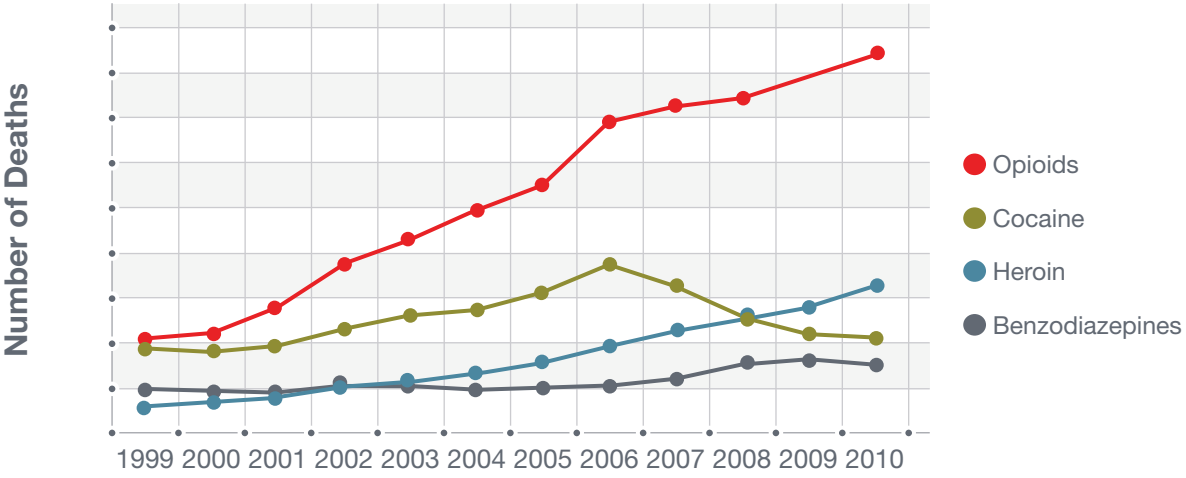


Figure 1:
The number of deaths due to opioid and benzodiazepine overdose have increased in recent years, whereas there has been a decrease in deaths due to cocaine.

CDC/NCHS National Vital Statistics, CDC Wonder. Updated with 2010 mortality.

Growth in Opioid Prescriptions

A strong correlation exists between the number of deaths from opioid use/abuse and the number of retail opioid prescriptions from the past decade.[5]

Opioid Prescriptions[5]

by retail pharmacies in the United States IN MILLIONS

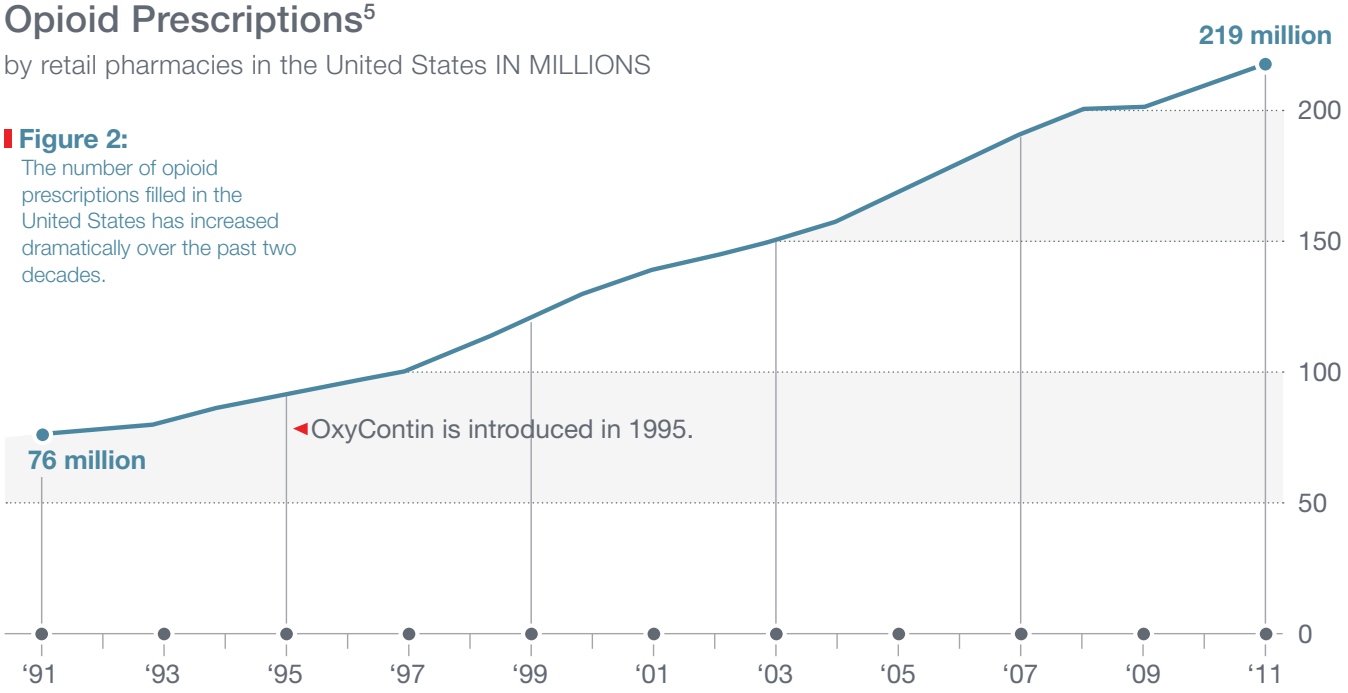


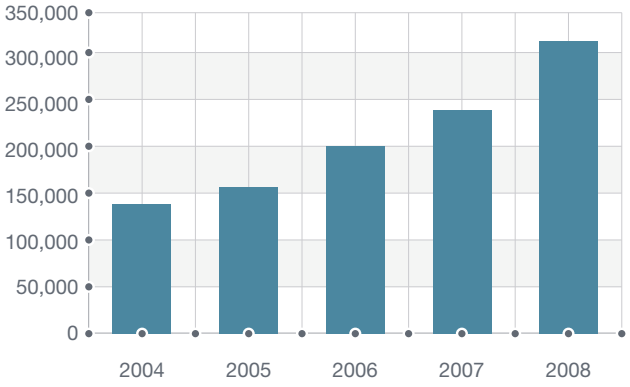
Figure 2:
The number of opioid prescriptions filled in the United States has increased dramatically over the past two decades.

Emergency Room Visits

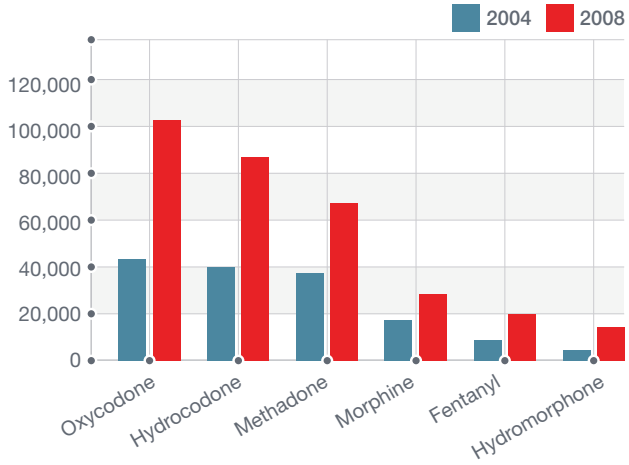
In addition to the concern over increased mortality rates associated with opioid prescriptions, opioid abuse is creating a tremendous economic burden on the healthcare system as a result of escalating emergency room visits. In 2011, approximately 1.4 million ER visits involved the non-medical use of pharmaceuticals. Among those ER visits, 501,207 visits were related to anti-anxiety and insomnia medications, and 420,040 visits were related to opioid analgesics.[7]

Abusers were 12.2 times more likely to have had at least one hospital inpatient stay, and four times more likely to have had an ER visit. Opioid abusers average 18.7 physician or outpatient visits, compared with seven for non-abusers. Opioid abusers averaged 41.6 prescription drug claims each, compared with 13.8 for non-abusers.[6]

ER Visits Caused by Abuse of Narcotic Painkillers

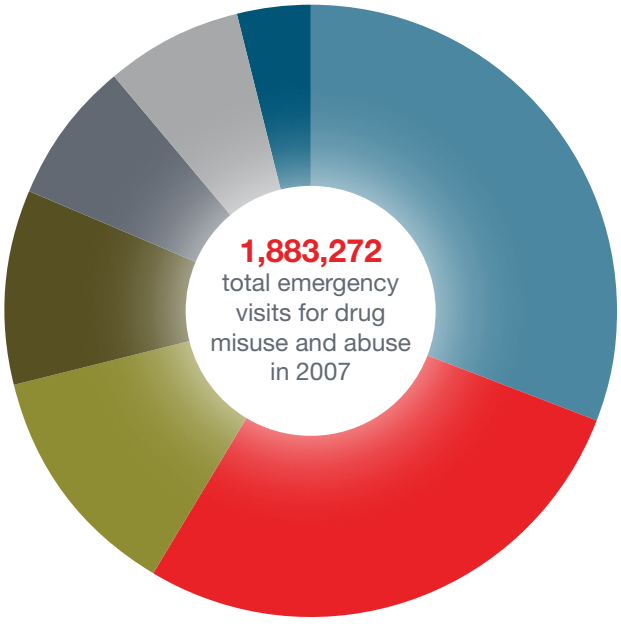


ER Visits Caused by Abuse of Certain Painkillers, 2004 - 2008



Emergency Room Visits Caused by Drug Misuse and Abuse in 2007, by Combination

- Nonmedical use of pharmaceuticals only (30.9%)
- Illicit drugs only (27.8%)
- Illicit drugs; alcohol (12.6%)
- Alcohol; nonmedical use of pharmaceuticals (10.1%)
- Illicit drugs; pharmaceuticals (7.6%)
- (Underage) Alcohol only (7.3%)
- Illicit drugs; alcohol; pharmaceuticals (3.7%)



history of drug testing

Drug screening in the USA began in the 1970s as an attempt to mitigate the spread of drug abuse in the US military forces stationed in Vietnam. The Navy started screening after an accident on the carrier Nimitz revealed that a number of sailors and airmen were taking mind altering drugs. Before the start of drug screening in the U.S. military, surveys showed a prevalence of drug use at 47%. When random testing was begun, the positive rate was 22%, a figure which steadily declined every year to 2.5% after six years of testing and to less than 1% today.[8] Although these numbers were specific to military drug testing, the efficacy of random drug testing illustrates the impact that implementing a drug testing solution can have in preventing drug misuse.

immunoassay

Immunoassay testing has inherent technological shortcomings, creating a level of uncertainty in drug test results. Although it was invented in the 1940s, immunoassay technology wasn't really introduced on a broad scale until 1973. Immunoassay uses light-emitting chemicals bound to antibodies that are intended to bind to the drug of interest. This technology employs an indirect measurement of the drugs or drug classes by utilizing the chemical properties of the drugs of interest and their innate ability to bind to the light-emitting labeled antibodies. Since this measurement and technique is indirect, its specificity is less than optimal and raises a rather high level of scrutiny and its reliability has been questioned.

False positives results can occur when similar structural characteristics of dissimilar compounds bind to the light-emitting antibodies and emit a positive response. False positives can be confirmed and thus pose less of a threat than false negatives.

False Negatives and Cutoffs

False negative results occur when the concentration of the analyte being tested is lower than the laboratory's ability to detect it. The time since drug usage, the amount and frequency of use, fluid intake, body fat level, and metabolic factors can affect the urine drug concentration.

False Positives and Cutoffs

The administrative concentration cutoff ranges depend on the technology available, as well as what is clinically important for the application. The performance traits of the reagents are very important when considering assay cutoff levels. Cross reactivity is when the binding site of dissimilar compounds are similar and thus binding to the labeled antibody. This causes a reading that is translated to a result, thus causing a positive result. Whether or not it is a similar compound to the target or completely different is undiscernible by reviewing the immunoassay data. This inherent, and well researched, issue is responsible for guiding cutoff levels to prevent too many false positives.

For example, the cross reactivity of target compounds including but not limited to codeine, morphine, amphetamine, and methamphetamine may cause the assays' cutoff level to range higher than the confirmatory cutoff because, in many cases, these thresholds are set to minimize the potential error that is exacerbated by poor result interpretation. For instance, the initial cutoff which was established for opiates in these programs was set up to 300 ng/mL, which was revised to 2000 ng/ml in the year 1994 to lower the number of positive results that had lower morphine concentration due to ingestion of poppy seeds in certain foodstuff. SAMHSA has attempted to set cutoff levels high enough to minimize false positive results.[10] However, drug use patterns follow all types of trends, and do not necessarily reach ultra-high levels before drug use is considered a serious threat to one's health and to society as a whole.

gas chromatography-mass spectrometry (GC-MS)

In 1966, as the immunoassay test was being developed, Manfred Donike pioneered the use of gas chromatography-mass spectrometry (GC-MS) to detect anabolic steroids and other prohibited substances in athletes' urine. Donike began the first full-scale testing of athletes at the 1972 Summer Olympics, in Munich, using a GC-MS linked to a Hewlett Packard computer. At the 1983, Pan American Games, Donike's laboratory disqualified 19 athletes and caused numerous others to withdraw before they were due to be tested. During the 1988 Summer Olympics, his testimony led to the suspension of Canadian sprinter Ben Johnson even though there were claims that drugs were spiked in sports drinks.[11]

liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS)

Since GC-MS was the first mass spectrometry testing methodology and the cost of a GC-MS was one-fifth of the cost of liquid chromatography tandem mass spectrometry (LC-MS/MS) technology at the time, GC-MS became the industry standard. During the early 2000s, LC-MS/MS technology greatly improved in sensitivity, robustness, and reproducibility. By 2005, as clinical and toxicology testing was becoming widely adopted, LC-MS/MS manufacturers were selling instrumentation that gained equivalency to GC-MS's sensitivity levels.

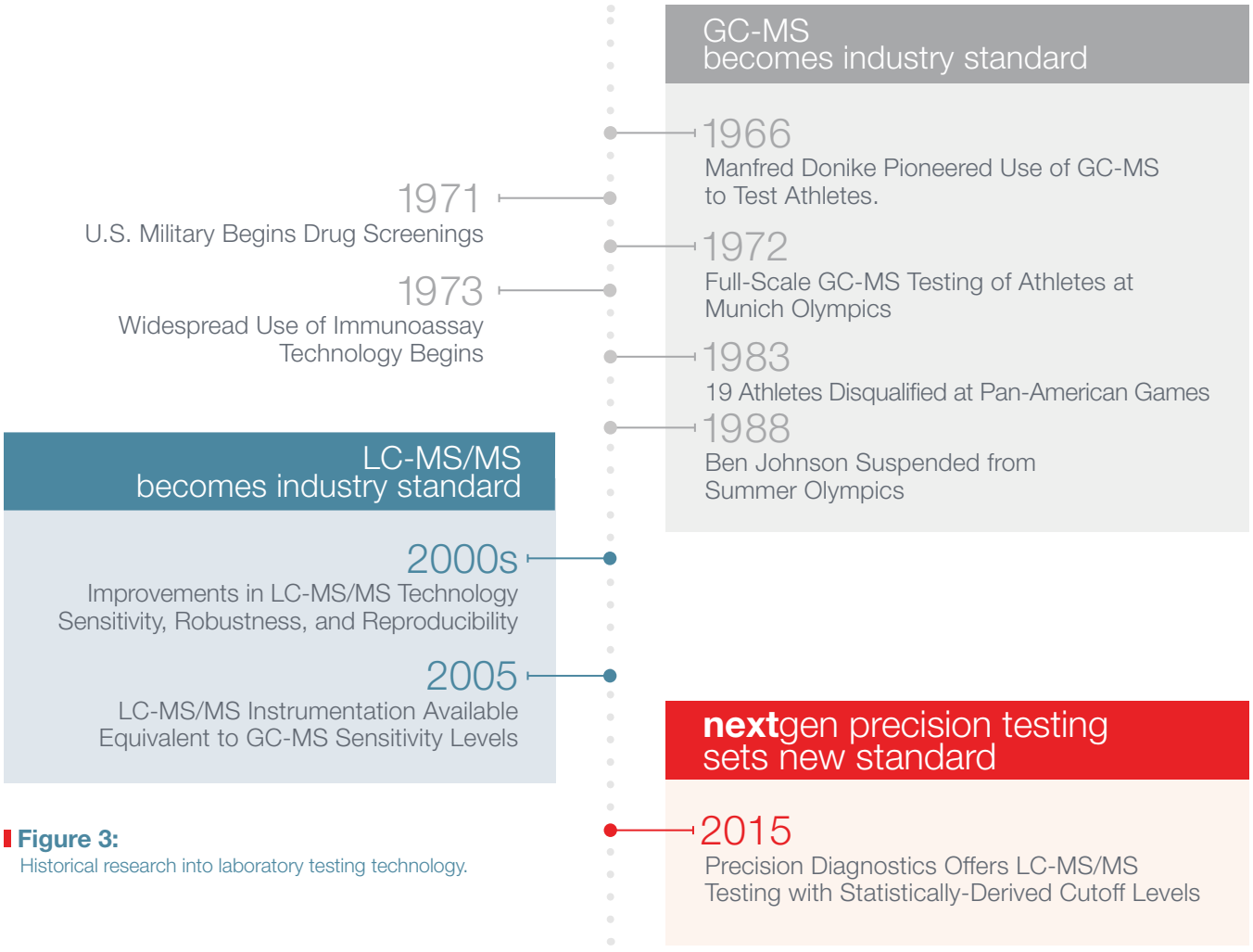


Figure 3:
Historical research into laboratory testing technology.

questioning usual and customary cutoff levels

With the increase in information available to the general public on how to create uncertainty in drug test results, the tools used to identify drug misuse and diversion must evolve as well, to remain technically relevant and applicable. Medical imaging technology has continually evolved to improve diagnostic sensitivity and accuracy. In a similar way, clinical drug testing monitoring technology (and methodologies) should continually improve to deliver the best possible results and outcomes.

In a letter titled "What Congress and the Next Administration Must Do to Save Drug Testing", written by the chairman of the American Association of Medical Review Officers (AAMRO), Theodore F. Shults, JD, MS brought this to the attention of the Substance Abuse and Mental Health Association (SAMHSA), an agency that determines appropriate drug test cutoff levels for the industry. In this letter he stated "…there is an astounding number of false-negative results caused by the failure of SAMHSA to adopt lower cutoff values for cocaine, amphetamine and THC (not including the unknown number of specimens that are really substituted)." Additionally, in this letter, it suggests that sources indicate that SAMHSA has not improved their technology since the 1980s — and yet the drug testing industry is still using these technologies as the basis to address the drug epidemic in the United States.

> **"... there is an astounding number of false-negative results caused by the failure of SAMHSA to adopt lower cutoff values for cocaine, amphetamine and THC ..."**
>
> *– Theodore F. Shults, JD, MS*

Upon recognizing that the GC-MS and standard LC-MS/MS cutoff levels were potentially resulting in a large number of false negative test results, Precision Diagnostics investigated various research grade LC-MS/MS instrumentation to properly address the drug testing offerings that have been dogma for many years. Precision Diagnostics' goal was to identify what drug cutoffs should be if sensitivity was not limited by technology.

methods

A retrospective analysis of 46,717 human urine samples was performed to determine the appropriate clinical cutoff concentration for common over the counter, prescription, and illicit drugs in the patient population currently served by Precision Diagnostics.[12] All concentrations were determined by LC-MS/MS analysis. A histogram of patient results was created on a logarithmic x-axis of concentrations in nanograms of analyte per milliliter of urine (ng/mL). The frequency of results found in each grouping were plotted on the y-axis and a trend line was applied to drugs with greater than 200 positive patient results, which formed a normal distribution, at the intersection of the x-axis intersection to determine the appropriate cutoff for future clinical testing.

results

Precision Diagnostics determined that our current cutoff levels were suboptimal for 34 of the 39 drugs in our current test panel that occurred often enough to form a normal distribution. Twelve drugs were present in insufficient numbers for analysis. For EDDP, the metabolite of methadone, we actually determined that our current cutoff level was lower than necessary to achieve 99% coverage on the normal distribution curve. In the vast majority of drugs for which we test, however, we determined that our current cutoff levels were higher than necessary to achieve satisfactory coverage on the low end of the normal distribution curve and that we needed to significantly lower our cutoff level in order to achieve adequate coverage.

Methadone Analysis

Methadone is an example of a drug for which our current cutoff level was set appropriately to avoid false negatives within our patient population. The histogram of patient results shows a normal distribution or "bell curve." The trend line applied to the data crosses the x-axis at approximately 75 ng/mL. Excluding all patient results below that level would remove 1% of likely positive results.

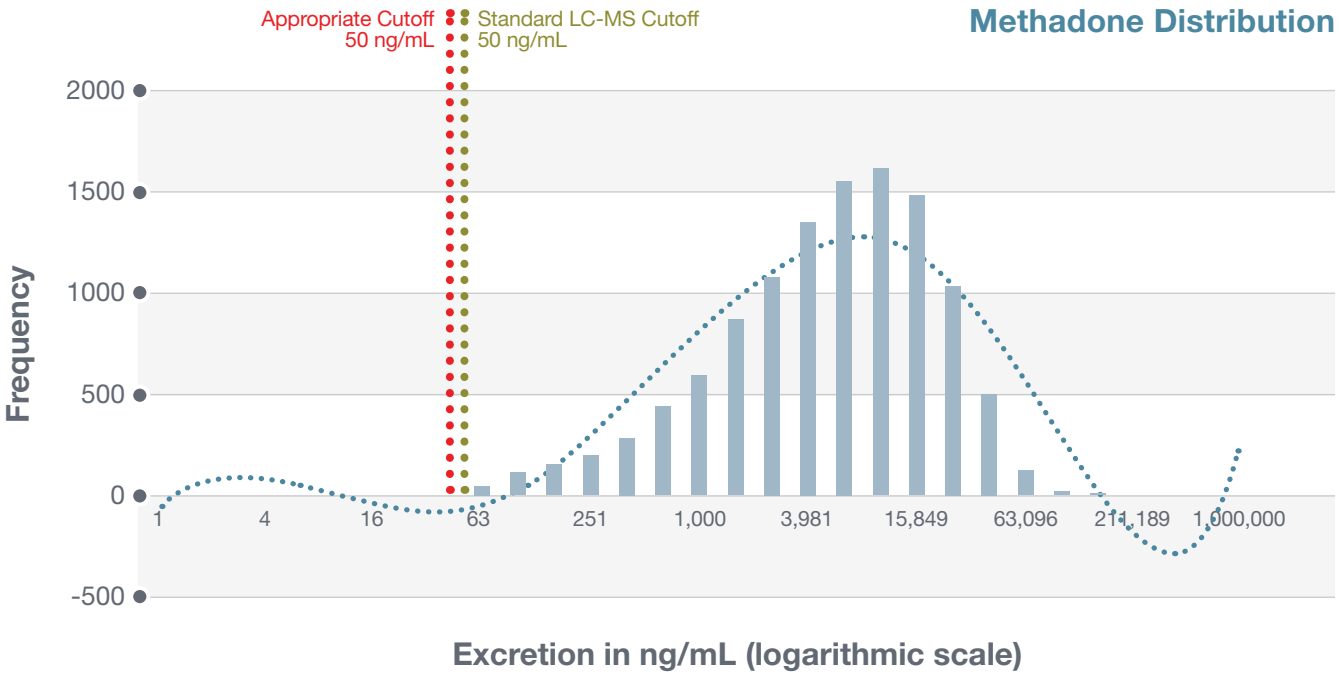


Figure 4:
The excretion profile of methadone follows a normal distribution with a trend line applied to find the cutoff level which would result in approximately 99% coverage of likely positive samples.

Alprazolam Analysis

In the analysis of alprazolam on a normal distribution plot, the left side of the curve is truncated, indicating an inappropriately set cutoff level. The current cutoff of 50 ng/mL causes likely positive patient results to be reported as negative. The trend line crosses the x-axis at approximately 5 ng/mL, indicating a more appropriate clinical drug test cutoff level. In this case, the industry standard cutoff level was woefully inadequate in identifying a large number of positive test results for alprazolam, resulting in a significant number of false negative test results.

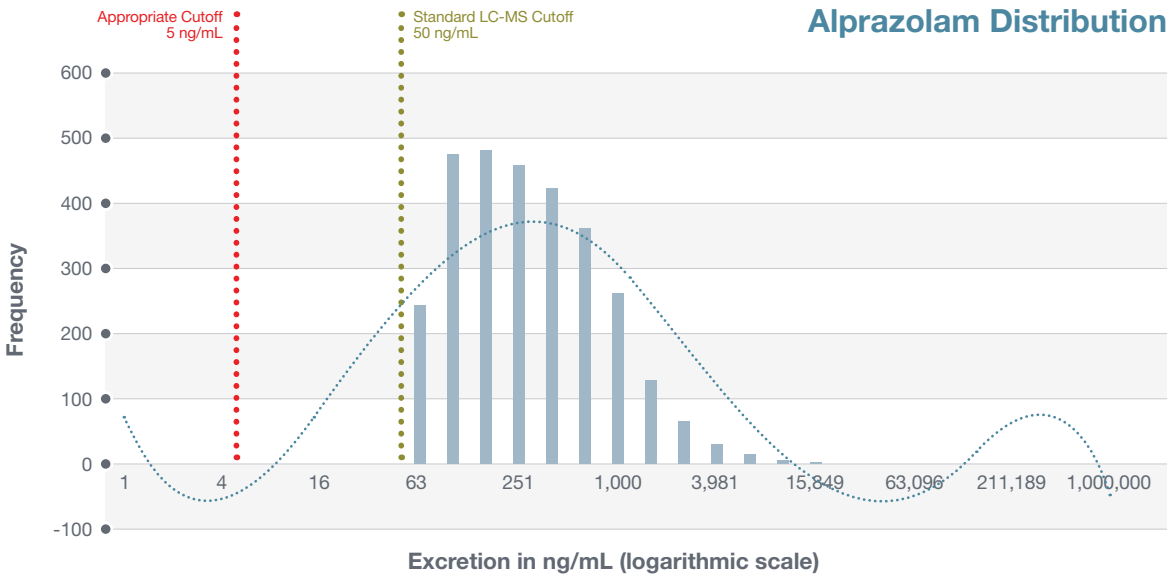


Figure 5: The distribution of patients' results for alprazolam demonstrates that 50 ng/mL is an inappropriate cutoff level for alprazolam, and that a lower cutoff level would be more clinically relevant.

Amitriptyline Analysis

Amitriptyline is a widely prescribed tricyclic antidepressant and is intended to be taken every day to manage symptoms of depression. Long term adherence to the regimen is vital to the patient's health and must be monitored during treatment. The industry standard cutoff level of 100 ng/mL is insufficient for about half of patients who are taking amitriptyline. A myriad of issues are caused by the false negative results, including decreased doctor-patient trust and ascribing depressive symptoms to medication non-adherence rather than other causes.

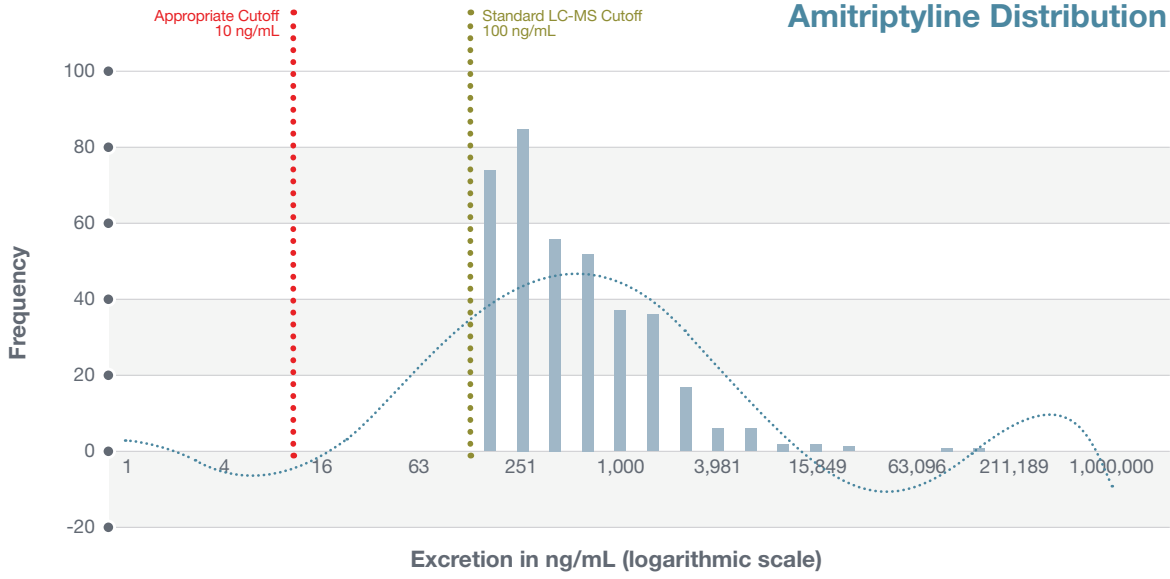


Figure 6: Amitriptyline's distribution appears to reach a maximum at the 100 ng/mL cutoff, indicating that an equal number of likely positive patient samples are being reported as negative.

Cyclobenzaprine Analysis

For the analytes cyclobenzaprine, amitriptyline, clonazepam, nordiazepam, nortriptyline, and zolpidem, half or fewer of the expected positive patient samples were identified with our current cutoff levels. This was a very alarming finding of this retrospective analysis. Based on our statistical analysis, these compounds have the greatest need for higher sensitivity analysis so that positive results are not missed.

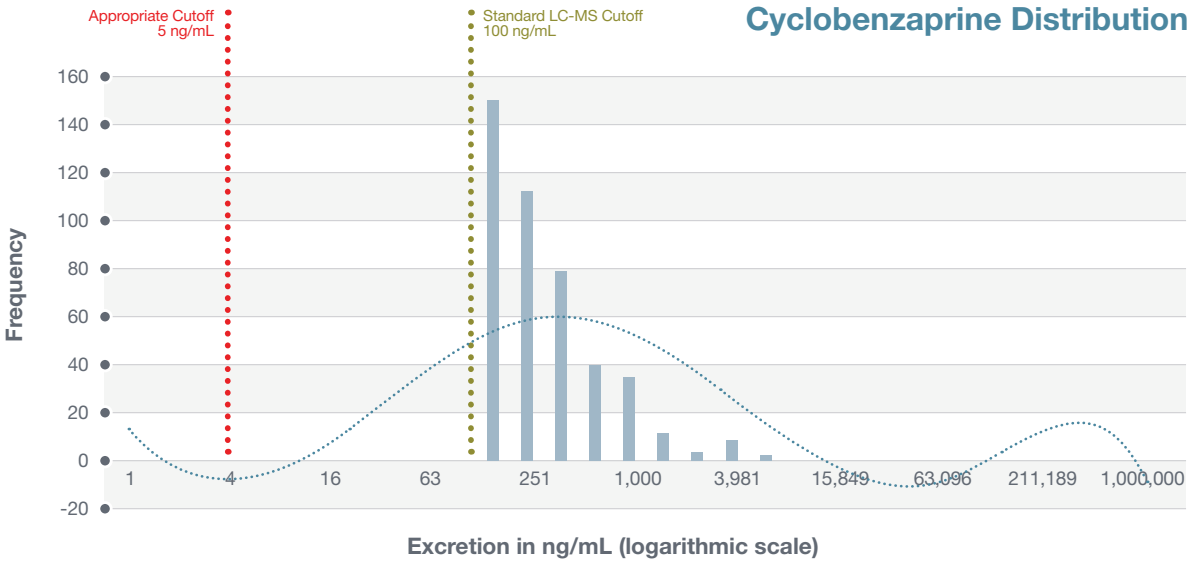


Figure 7: Cyclobenzaprine's distribution does not reach a maximum value, indicating the need for a significantly reduced lower cutoff limit of quantitation for this compound. If it follows a normal distribution, greater than 50% of positive samples are not being identified through current cutoff levels.

Zolpidem Analysis

Zolpidem is prescribed to treat insomnia, but can also be used recreationally for its ability to induce euphoria and vivid visual effects. Its usage is contraindicated by opioids, alcohol, benzodiazepines and other medications. The distribution of positive results shows a truncated left side of the bell curve indicating a lower cutoff level should be used.

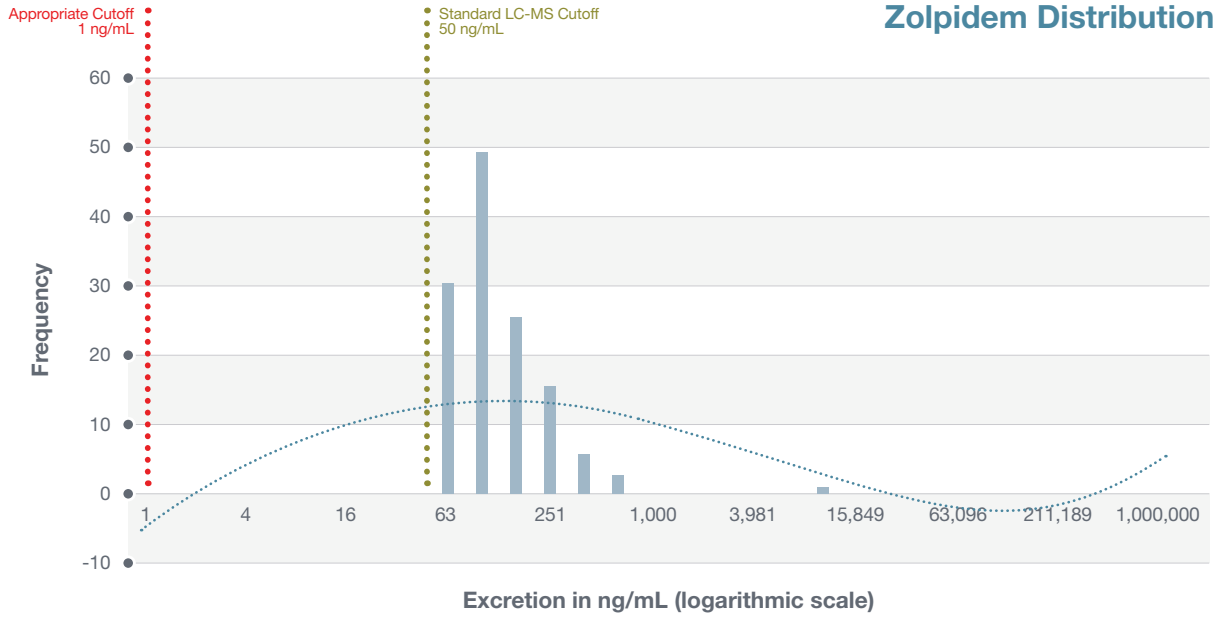


Figure 8: Zolpidem's distribution analysis shows that a cutoff level lower than 50 ng/mL should be used to identify more positive patient results. NextGen Precision uses a 1 ng/mL cutoff level.

cutoff level comparison summary

The table below illustrates drugs within the analysis that routinely tested positive as well as a cutoff level comparison from the evolved NextGen Precision cutoff levels. This table also illustrates the estimated percentage of false negatives using current cutoff levels versus the newly recommended NextGen Precision cutoff levels.

NextGen Precision Testing Analysis

	Cutoff Level Comparison			False Negative Analysis	
Drug Name	Industry Standard Cutoff Levels	NextGen Precision Cutoff Levels	% Increase in Sensitivity	Est % False Negatives Old Cutoff vs. NextGen Cutoff Levels	Est % NextGen False Negatives*
Alphahydroxyalprazolam	50	5	900%	40%	<1%
Alprazolam	50	5	900%	40%	<1%
Nordiazepam	50	5	900%	90%	<1%
Temazepam	50	10	400%	15%	<1%
7-Aminoclonazepam	50	5	900%	20%	<1%
Lorazepam	50	10	400%	10%	<1%
Oxazepam	50	10	400%	20%	<1%
6-Acetylmorphine	25	5	400%	25%	<1%
Benzoylegonine	50	5	900%	10%	<1%
Methamphetamine	100	10	900%	25%	<1%
Amphetamine	100	25	300%	15%	<1%
Codeine***	50	50	0%	10%	<10%
Hydrocodone	50	5	900%	5%	<1%
Norhydorcodone	50	10	400%	5%	<1%
Oxycodone	50	10	400%	5%	<1%
Noroxycodone	50	25	100%	2%	<1%
Morphine***	50	50	0%	10%	<10%
Hydromorphone	50	5	900%	35%	<1%
Oxymorphone	50	10	400%	10%	<1%
Fentanyl	5	1	400%	10%	<1%
Norfentanyl	5	2	150%	10%	<1%
Buprenorphine**	10	5	100%	5%	<1%
Norbuprenorphine**	10	5	100%	1%	<1%
Naloxone	100	10	900%	35%	<1%
Methadone	50	50	0%	1%	<1%
EDDP	50	100	-50%	1%	<1%
Carisoprodol	100	10	900%	30%	<1%
Cyclobenzaprine	100	5	1900%	50%	<1%
Meprobamate	100	100	0%	1%	<1%
Tramadol	50	25	100%	5%	<1%

Table 1: A comparison of cutoff levels and their estimated percentage of false negatives and the percent improvement resulting from applying a new statistically derived lower cutoff level using NextGen Precision Testing.

With the exception of methadone, EDDP, meprobamate, codeine, morphine and norbuprenorphine, there is an average estimated improvement of 90% that results from shifting from the standard cutoff levels to our new NextGen Precision statistically-derived cutoff levels. In order to achieve this 90% improvement, we had to increase the sensitivity by 900% in many cases. For those drugs where decreasing the cutoff levels did not appear to impact our estimated improvement, the cutoff levels remained the same. In fact, EDDP cutoff levels were actually increased as current cutoff level of 50 ng/mL does not appear to improve clinical data more than 100ng/mL.

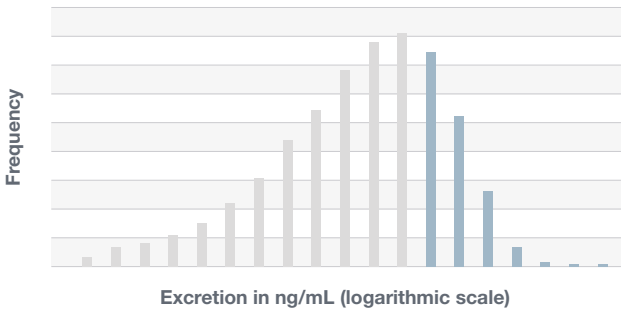
*Projected false negatives based on the data extrapolated from our pooled patient population in this study. **For clinics that treat with transdermal buprenorphine at µg/day doses, this data does not apply. *** Codeine and Morphine were not adjusted due to potential environmental exposures such as poppy seeds.

NextGen Precision vs. Standard LC-MS/MS and Immunoassay Cutoff Levels

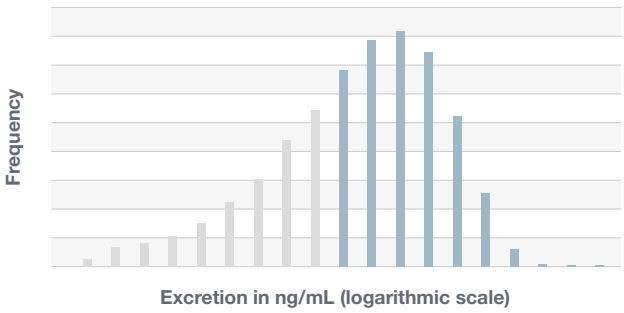
A secondary goal of the analysis was to evaluate the new NextGen Precision cutoff levels compared to the standard LC-MS/MS cutoff levels, as well as how they compare to typical immunoassay cutoff levels. This was done to determine what the theoretical false negative percentage is across the three different assays for a given drug analyte. We looked at alprazolam, as it is a commonly prescribed drug to treat anxiety disorders and also has a high abuse potential.

The following charts show the normal distribution curve for our patient population and where the cutoff level for each testing methodology lands on the normal distribution curve.

Alprazolam: Immunoassay



Alprazolam: Standard LC-MS/MS



Alprazolam: NextGen Precision Testing

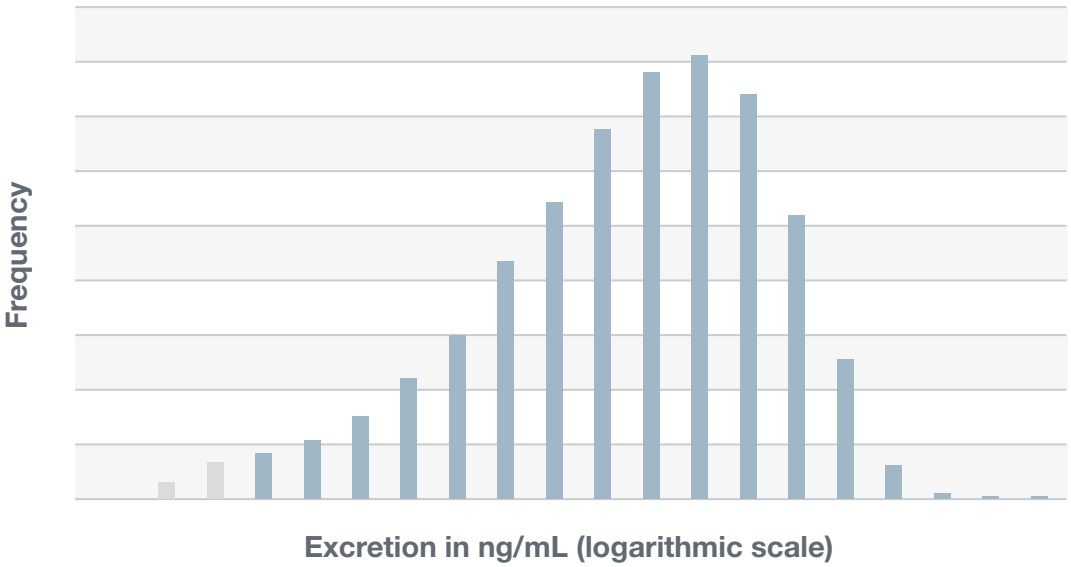


Figure 9:
The results histogram for alprazolam contrast three methods to test for its presence. The blue bars represent positive patient results that can be expected using immunoassay (300 ng/mL cutoff level), standard LC-MS/MS (50 ng/mL cutoff level) and NextGen Precision (5 ng/mL cutoff level). The grey bars represent false negative patient results.

conclusion

Precision Diagnostics' retrospective analysis of patient test result data concluded that industry standard cutoff levels were not appropriately set to identify a significant number of positive test results that were otherwise being reported as negative. False negatives can occur as a result of inappropriately set drug cutoff levels and limitations in technology for both qualitative and quantitative testing. This can ultimately cause providers to make an unnecessary change in treatment planning.

This analysis was the impetus in launching NextGen Precision Testing. Developed to improve clinical data through statistically derived cutoff levels that leverage advances in LC-MS/MS technology, NextGen gives healthcare providers the best possible information to improve outcomes and patient satisfaction.

As the cost and health risks associated with drug misuse, abuse, and diversion continue to grow, technology used for clinical drug monitoring should evolve to address healthcare trends. Results of the statistical analysis of 46,717 urine samples indicate that NextGen Precision Testing represents the next step in delivering comprehensive insights providers need to improve outcomes for their patients.[12]

for more information

regarding Precision Diagnostics' NextGen Precision Testing solution, please call us at 800.635.6901 or email info@precisiondxlab.com

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transforming healthcare through clinical laboratory science

Precision Diagnostics is a leader in clinical laboratory testing and medication adherence monitoring. Our NextGen Precision Testing platform employs ultra-sensitive LC-MS/MS technology in a fully automated, robotic facility.

Specializing in qualitative and quantitative drug testing, our innovative state-of-the art technology provides new levels of data visibility and pricing transparency. Precision's role is to ensure each participant, from the patient to the provider and the payor, benefits from our continued commitment to the principles of value-based care and medically necessary test utilization.

INNOVATION

We are committed to pursuing research, technology, compliance, and quality – providing unparalleled clinical laboratory science and delivery.

INTEGRITY

We incorporate only ethical business solutions representing the highest quality standards, rooted in the principles of value-based care and medically necessary test utilization.

INSIGHTS

We integrate and deliver intelligent data that powers objective, actionable clinical data – fulfilling our commitment to transforming healthcare.

OUTCOMES

We continually explore new advances in delivering informed, coordinated, and efficient care that leads to improved patient outcomes.

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