



Cotinine Testing: Be more cost-effective and reduce uncertainty

Objective Maximize sensitivity of cotinine testing to find un-admitted nicotine use and maximize specificity to reduce conflicts and exceptions. This is CRL proprietary information for internal use at your company only.

Background Cotinine is a specific metabolic breakdown product of nicotine that is excreted in the urine. Unlike nicotine, cotinine remains present in the urine for many hours after a tobacco or other nicotine-containing product is used. The lower limit for cotinine positivity has traditionally been set at 500 ng/ml (0.5 µg/ml). However, many admitted tobacco users have levels below this suggesting that some who deny use and have levels that are detectable but below 500 ng/ml are also likely nicotine users.

In addition to missing nicotine users and collecting insufficient premium, some applicants deny use in the face of a “positive” cotinine result. The degree to which one should believe such protestations is unclear. Cotinine is routinely analyzed using relatively inexpensive antibody screens at all industry laboratories which, like most antibody screens, can be subject to false positives. Lowering the 500 ng/mL cut-off to improve sensitivity to nicotine use would worsen this specificity problem.

Facts CRL conducted a study on cotinine. Looking at 3 million applicants who reported no tobacco use, CRL found the following percentages of all and “non-tobacco” applicants at listed levels of urine cotinine:

| Cotinine ng/mL | % of all Applicants | % “Non-tobacco” |
|---------------------------|---------------------|-----------------|
| 0-200 | 85.81 | 95.5 |
| 201-500 | 1.13 | 0.8 |
| 501-1,000 | 1.27 | 0.7 |
| >1000 | 11.79 | 3.1 |
| Total 201 ng/mL or higher | | 4.6 |

Potentially 1.13% of all applicants are misclassified as non-tobacco if 500 ng/mL is used as an absolute cut-off rather than the lower 200 ng/mL.

To discover how many of those with cotinine in the urine but indicating no tobacco use were truthful, GC/MS confirmation was done on 455 samples. This is the gold standard of urine drug testing. The following results were noted:

| Urine Cotinine ng/mL | GCMS Confirmation | | |
|----------------------|-------------------|----------|------------|
| | Negative | Positive | % Positive |
| 100-200 | 50 | 2 | 3.85 |

| | | | |
|----------|----|-----|--------|
| 201-500 | 32 | 100 | 75.76 |
| 501-1000 | 20 | 97 | 82.91 |
| >1000 | 0 | 144 | 100.00 |

Below 201 ng/mL, almost all positives are false positives and between 201 ng/mL and 1,000 ng/mL, 17 to 24% are false positives in those claiming to be non-tobacco. Above 1000 ng/ml, all positives are true positives. Little tobacco use is missed with a cut-off of 200 ng/mL but 0.75% of all applicants are being misclassified as non-tobacco if 500 ng/mL is used. In addition, between 200 and 1,000 ng/ml, 17-24% of applicants who deny use appear to be truthful.

The remaining question is if levels below 500 ng/mL represent nicotine exposure, could they be environmental rather than intentional use? The world literature was reviewed and it was found that the highest level ever noted from occupational exposure was 197 ng/mL in casino workers in 1996. The highest non-occupational exposure noted was 32.3 ng/mL. Even this decade-old extreme occupational exposure, unlikely to be present currently, fell below the 200 ng/mL cut-off and non-occupational exposure was always well below.

Cost benefit analysis was performed assuming a cost of GC/MS confirmation to be \$25. Based on smoking and non-smoking premium, modest savings were generated by using a testing protocol where the cotinine cut-off was set at 200 ng/mL and all samples between 200 and 1,000 ng/mL where the applicant denied smoking on the lab authorization were confirmed by GC/MS. In addition to savings, the roughly 17% of applicants with screening values between 500 and 1,000 ng/ml currently labeled as smokers were also correctly classified as non-smokers avoiding conflict, exceptions, ill will and lost policies.

Conclusions

- ◆ Using a cotinine cut-off of 500 ng/mL without confirmation testing results in missing a significant number of nicotine users and creating false positives.
- ◆ The cut-off for considering cotinine positive (nicotine user) should be set at 200 ng/mL (0.2 µg/ml).
- ◆ Values between 200 ng/mL and 1,000 ng/mL should be confirmed by GC/MS if the applicant indicates non-smoking status on the laboratory authorization. This affects approximately 1.3% of applications.
- ◆ The above steps are cost effective and, as importantly, accurately classify applicants as to nicotine use eliminating a common conflict and avoiding lost policies due to false positives.