IMPROVEMENTS IN COTININE TESTING OF INSURANCE APPLICANTS

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Executive Summary: Approximately 0.8% to 2% of applicants are being misclassified as non-tobacco users. These applicants misrepresent their tobacco use status and their cotinine levels fall below the currently established cotinine threshold. This misclassification is costing insurers premium income as these applicants are being charged non-tobacco rates. The amount of misclassification can be reduced by lowering cotinine screen thresholds. Ninety-five percent (95.45%) of all applicants applying as non-tobacco users are negative in the initial screening assay; of the 4.55% initially positive, 93% confirm as positive by GC/MS. This is equivalent to 0.32% of the population testing false positive (7% x 4.55% = 0.32%). Our data show that approximately 7% of non-tobacco using applicants who are cotinine positive at current cut-offs and "declare" they do not smoke are truthful. To avoid even this low number of false positives, confirmatory testing should be done on all samples with low levels of cotinine from applicants applying as non-tobacco users. If the cut-off changes to 200 ng/ml (0.2 µg/ml), the number affected by this recommendation is about 1.4% of the tested population.

Challenges

The screening test for tobacco use is antibody-based, which is very reliable when there is a relatively large amount of cotinine. The test becomes less reliable when the amount of cotinine in the fluid is close to the limits of detection, which includes cotinine values less than 100 ng/ml (0.1 µg/mL).

Because of this, the threshold for being considered a true tobacco or other nicotine user based on cotinine level is set artificially high to decrease the risk of misclassification, even though it may not be completely eliminated. This higher threshold allows some tobacco users to escape identification by life insurers.

When the cotinine positive applicant denies tobacco use, doubt can arise about the screening test validity. Common explanations offered by applicants for positive levels of cotinine besides tobacco use include:

- Exposure to large amounts of environmental (second-hand) tobacco smoke;
- Consumption of food contaminated with nicotine-containing pesticide; and
- Consumption of teas or betel that contain tobacco.

Solutions

The following actions are suggested by the authors to address these issues:

- Lower the screening test threshold for a positive result. This will improve the screening test sensitivity in detecting tobacco users.
- Keep the screening test threshold for a positive cotinine result high enough to effectively exclude those who are exposed to nicotine solely through exposure to environmental tobacco smoke.
- Confirm all positive screen results in which the applicant denies tobacco or tobacco substitute use with a more definitive test for cotinine. This will maximize specificity in detecting only true tobacco users.

Cotinine Screen Results for Admitted and Denied Tobacco and Tobacco Substitute Users

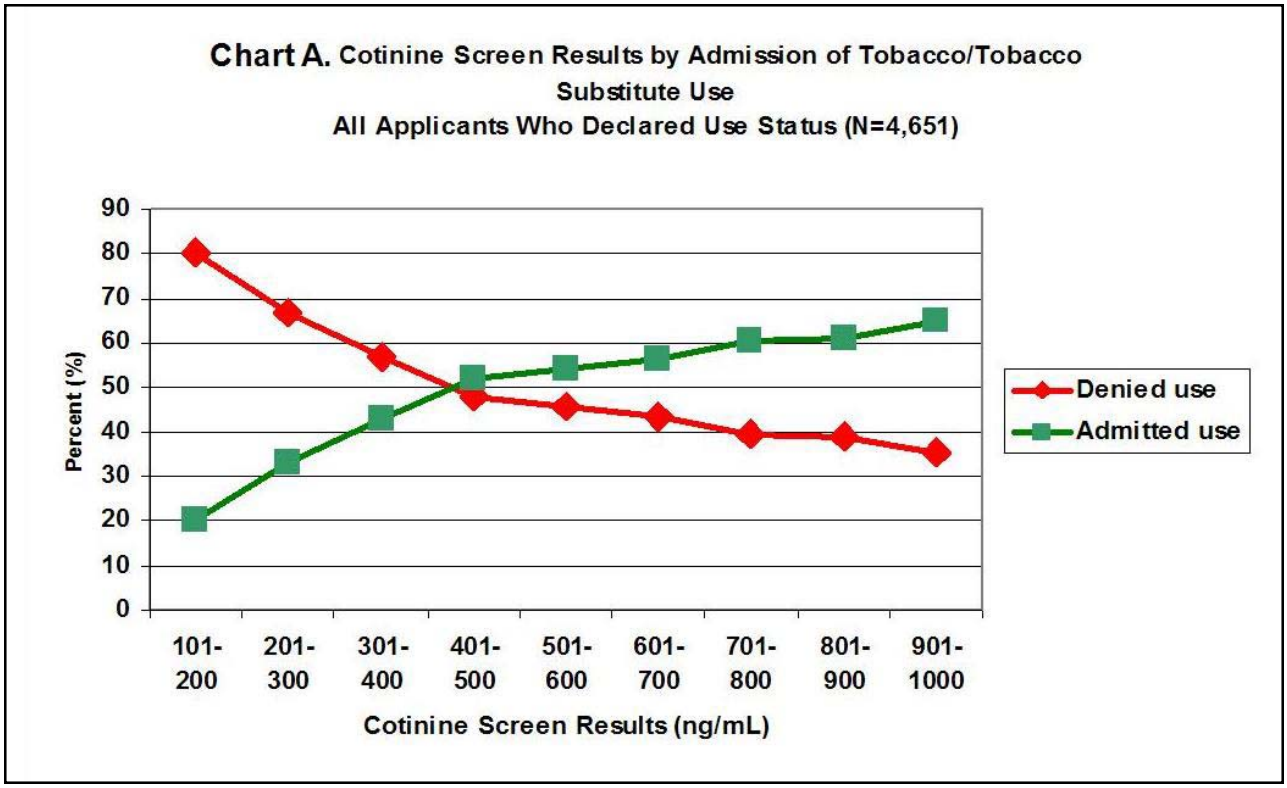
The standard CRL consent form contains three questions about tobacco use; over 97% of applicants declare their tobacco use status. The authors studied the relationship between cotinine screening results and GC/MS confirmation results for applicants who disclosed their use status and who had screening test values between 100 ng/ml and 8,000 ng/ml.

Chart A shows levels of cotinine detected by self-reported tobacco status for 4,651 applicants. All those with lower results (typically below 500 ng/mL) are currently considered nonusers, and those with higher results are considered users. The proportion of applicants admitting tobacco or other nicotine use increases steadily with increasing cotinine screen levels. However, there are admitted tobacco users with cotinine screen results down to 100 ng/mL even though the proportions of admitted users decrease with decreasing cotinine screen results.

The Confirmation Test for Cotinine

The gold standard for confirmation of drugs is gas chromatography/mass spectrophotometry (GC/MS) or liquid chromatography/mass spectrophotometry/mass spectrophotometry (LC/MS/MS). Both methods can precisely quantify the amount of cotinine in the fluid being tested. Either test is more expensive than the antibody-based cotinine screen test, so they will be used only on a select basis as needed.

The situation in which a GC/MS test would be most useful is when a cotinine screen result is positive and disputed by the applicant. In this case the sample would be tested with GC/MS, giving a definitive answer about the cotinine level of the sample.



To better understand the pattern of positive and negative test results, the prevalence for tobacco use was determined in a large population of insurance applicant urine samples. Over 3 million samples were included in the analysis; analysis was for both the total applicant population and the portion that had self-reported no tobacco use. The summary data are presented in *Table 1* (next page).

Ninety-five percent of self-reported non-tobacco users are negative in the initial screen for urine cotinine. Of applicants applying as non-tobacco users, 4.55% were positive (> 200 ng/mL) in the initial screening test for cotinine. If the positive cut-off were lowered to this level, 1.46% (0.80 + 0.66) of the total applicant population would require confirmation testing.

To evaluate the usefulness of the cotinine GC/MS test, CRL performed a study on life insurance applicants in 2005. Confirmatory GC/MS tests of cotinine were performed on 445 applicants who tested positive for cotinine in the antibody-screening test, and had levels of cotinine between 100 and 8,000 ng/mL. These applicants had declared on their insurance applications they did not use any tobacco.

[See *Table 2* next page.]

Out of 132 screening test results between 201 and 500 ng/mL, 100 (75.76%) were confirmed as posi-

Table 1 - The level of cotinine detected in insurance applicants who self-reported no tobacco used.

Cotinine ng/mL	Number of Applicants	% of all Applicants	% of self-reported Non-tobacco
0-200	2,678,700	85.81	95.45
201-500	35,429	1.13	0.80
501-1,000	39,597	1.27	0.66
>1,000	367,998	11.79	3.09
Total Positive (>200 ng/mL)		14.19	4.55

Table 2 - GC/MS Confirmation of urine cotinine in 455 applicants who applied as non-tobacco users.

	GC/MS CONFIRMATION		
Urine Cotinine ng/mL	NEGATIVE	POSITIVE	% POSITIVE
100-200	50	2	3.85
201-500	32	100	75.76
501-1,000	20	97	82.91
>1,000	0	144	100

tive for cotinine. This means that over three quarters of applicants denying use with cotinine values between 201 and 500 ng/ml were tobacco users. These would be missed at the current 500 ng/ml cut-off for cotinine. GC/MS tests for confirming positive cotinine screen results between 201 and 500 ng/mL are thus helpful to correctly classify applicants who declare no tobacco use. Based on this study, using the GC/MS test will save about 25% of applicants in this situation from being undeservedly classified as tobacco users in this category.

Similarly, out of 117 screening test results that were between 500 and 1,000 ng/mL for applicants denying use of tobacco, 97 (82.9%) were confirmed as positive for cotinine. If the GC/MS test were used for similar applicants with cotinine screen results between 500 and 1,000 ng/mL, about 18% would be reclassified as non-tobacco users.

Combining those from 200 to 1,000 ng/mL, 79% of those denying use and positive on the screen were also confirmed positive by GC/MS.

For applicants with screening results greater than 1,000 ng/ml (100% of those denying use), all 144 were confirmed positive for cotinine by GC/MS.

Setting the Lower Limit to Avoid Labeling Non-Users Based on Environmental Exposure

The authors reviewed the world literature on cotinine levels associated with second-hand exposure in adults (data not shown but available on request). They found that the highest level ever found from occupational exposure was 197 ng/mL (casino workers in 1996). The highest level from non-occupational exposure was only 32.3 ng/mL. Moving the threshold for positive cotinine down to 200 ng/mL will correctly classify many tobacco users who are currently being misclassified while still eliminating those with second-hand exposure.

Conclusions and Recommendations

The authors recommend reducing the cotinine screening test threshold for a positive result from 500 ng/mL to 200 ng/mL. Samples with initial cotinine results between 200 ng/ml and 1,000 ng/ml will require confirmation testing by GC/MS if the applicant applies as a non-tobacco user. While all samples with screening results that exceed 1,000 ng/ml were confirmed as positive by GC/MS, any applicant who vehemently denies tobacco use should be confirmed with a more definitive test for cotinine, which is GC/MS.

Footnote:
The studies presented in this article reflect general CRL experience, and do not necessarily represent the experience of any particular insurer. The authors recommend that each insurer perform studies to estimate rates of tobacco misclassification, and likely rates for correct classification using new cotinine screening and confirmation testing thresholds.

Before adopting the new cotinine screening and confirmation testing thresholds, underwriting managers may wish to consider that the cost-benefit of any change in cotinine testing protocols depends on:

- The proportion of smokers among applicants, and
- The cost difference between smoker and non-smoker rates.

About the Authors

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