

# A Q-Probes Study Involving Utilization of Free Prostate-Specific Antigen, Factor V Leiden, and Hepatitis A Serology Tests

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• **Context.**—Managing the utilization of laboratory tests is an important quality improvement activity that adds value to health care.

**Objective.**—To examine utilization of 3 laboratory tests and identify factors that impact performance.

**Design.**—Test utilization performance was evaluated by determining the frequency with which appropriate preconditions for testing were met. This included 30 testing episodes each involving (1) free prostate-specific antigen (PSA) when total PSA was within an appropriate interpretable range, (2) total anti-hepatitis A virus antibody when previous anti-hepatitis A virus antibody results were either negative or not done, and (3) factor V Leiden mutation when a previous result was not already available. Participants also provided information regarding some of their utilization policies and procedures for these 3 tests.

**Results.**—The overall frequency with which testing

criteria were met was 20.6% (163 of 790), 91.5% (649 of 709), and 95.2% (799 of 839) for free PSA, anti-hepatitis A virus antibody, and factor V Leiden, respectively. Utilization review was infrequent and done by 20.7% (6 of 29) of participants for factor V Leiden, 3.6% (1 of 28) for anti-hepatitis A virus antibody, and 3.6% (1 of 28) for free PSA. No practice or demographic characteristics were significantly associated with utilization performance for any test.

**Conclusions.**—Utilization review was infrequent for the 3 tests examined. Variable amounts of unnecessary testing were observed for all tests, most frequently for free PSA, for which reporting results carried the added risk of diagnostic error from misinterpretation of results.

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Utilization management is an important component of laboratory quality improvement.<sup>1</sup> It involves understanding the gaps in laboratory testing practices that diminish value and that may even cause harm.<sup>2,3</sup> Utilization, as gauged by appropriateness criteria, can serve as an informative quality indicator of performance. Assessments may include frequency of testing (too often or infrequent), relevance (no additional value gained from testing), misordering (wrong test selected), or omission (incomplete testing).<sup>4</sup> This information can be used to drive improvements such as addressing operational issues (eg, misconfigured test menus)<sup>4</sup> or using decision support systems that promote good laboratory utilization practices.<sup>5,6</sup>

This Q-Probes study evaluated ordering practices for 3 tests as surrogates for evaluating utilization performance using preestablished appropriateness criteria rules. The first quality indicator involved redundant testing in which retesting provided no new information. Two tests used for this performance indicator included superfluous repeat orders for a genetic test (factor V Leiden [FVL]) and unnecessary repeat serologic testing for total anti-hepatitis A virus antibody (anti-HAV) when a previous test result was positive, indicating lifelong immunity. The other performance indicator was based on meeting a precondition based on results from a different test. In this case, the indication for measuring free prostate-specific antigen (PSA) was based on a prerequisite total PSA value necessary to reliably interpret results.

## METHODS

Participants in this College of American Pathologists Q-Probes study retrospectively collected data from 30 completed and verified results for each of the following tests: percentage of the free form of PSA, total anti-HAV, and FVL mutation. Participants provided their 2014 calendar year test volumes and testing locations (ie, on site or referred) for these 3 tests. Worksheets were provided to facilitate data collection. Appropriate utilization of the test was determined by the following criteria:

- Free PSA: Total PSA had been measured within the past 90 days and results were within the range specified by the testing

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**Table 1. Testing Practices and Characteristics of Participating Institutions**

Practice or Characteristic	% (No.)
Laboratory checks a patient's total PSA level before processing orders for free PSA (n = 29)	
Yes	3.4 (1)
No	96.6 (28)
Laboratory screens orders for FVL mutation testing for appropriate clinical indication (eg, history of thrombosis, age, risk factors) before processing (n = 29)	
Yes, always	13.8 (4)
Yes, sometimes	6.9 (2)
No	79.3 (23)
Laboratory automatically cancels or defers orders for FVL mutation testing if results from prior testing are documented (n = 29)	
Yes, automatically canceled	13.8 (4)
Yes, deferred until ordering provider is notified for final disposition	20.7 (6)
Yes, other	6.9 (2)
No	58.6 (17)
Laboratory restricts processing orders for anti-HAV antibody testing based on previous patient test results (n = 28)	
Yes	3.6 (1)
No	96.4 (27)
Total anti-HAV antibody is included on 1 or more viral hepatitis panels (n = 27)	
Yes	33.3 (9)
No	66.7 (18)
Tests included in hepatitis panel(s) with total anti-HAV test; multiple responses permitted (n = 9)	
Anti-HAV (IgM)	100.0 (9)
Hepatitis B surface antibody	77.8 (7)
Hepatitis C virus antibody	77.8 (7)
Hepatitis B surface antigen	66.7 (6)
Hepatitis B core antibody (total)	55.6 (5)
Hepatitis B core antibody (IgM)	33.3 (3)
Hepatitis Be antibody	11.1 (1)
Hepatitis Be antigen	11.1 (1)
Computerized provider order entry system used by majority of providers is capable of real-time display of prior test results (n = 30)	
Yes	40.0 (12)
No	60.0 (18)

Abbreviations: anti-HAV, anti-hepatitis A virus antibody; FVL, factor V Leiden; IgM, immunoglobulin M; PSA, prostate-specific antigen.

laboratory for which free PSA results could be reliably interpreted.

- Anti-hepatitis A virus antibody: No previous testing for anti-HAV had been performed within the last 3 years, or if testing had been done, all results were seronegative.
- Factor V Leiden: No previous testing for FVL had been performed within the last 3 years.

For free PSA testing, participants provided the lowest and highest total PSA levels used for interpretation of results. Participants recorded the corresponding total PSA measurement if performed within the last 90 days before free PSA was performed. Each free PSA measurement was also specified as reported either alone or as part of the calculated prostate health index (PHI) test. For each anti-HAV test, participants collected the total number of

**Table 2. Performance Indicators as Percentage of Cases Meeting Appropriate Utilization Criteria**

% of Cases Meeting Criteria	No.	All Institutions Percentiles				
		10th	25th	50th (Median)	75th	90th
Free PSA	28	0.0	3.3	13.3	33.9	63.3
Anti-HAV	24	82.4	86.7	93.3	96.7	100.0
FVL	28	83.3	91.7	98.4	100.0	100.0

Abbreviations: anti-HAV, anti-hepatitis A virus antibody; FVL, factor V Leiden; PSA, prostate-specific antigen.

any previously reported positive anti-HAV result(s) during a 3-year look-back period. Participants collected the total number of any previously reported FVL tests performed within the last 3 years. For each repeat test, participants reported whether or not results were concordant with each other.

Participants answered survey questions regarding their test utilization practices. Individual associations of the performance indicators and time intervals with the demographic and practice variables were analyzed using Kruskal-Wallis tests for discrete-valued independent variables and regression analysis for continuous independent variables. Variables with significant associations ( $P = .10$ ) were then included in a forward selection multivariate regression model. A significance level of .05 was used for this final model. We used  $t$  tests and  $\chi^2$  tests for the aggregate case results analyses. All analyses were performed using SAS v9.2 (SAS Institute, Cary, North Carolina).

## RESULTS

### Institution Demographics

Of the 30 institutions participating in the study, 29 (96.7%) were from the United States and 1 was from Brazil. Within the last 2 years prior to data collection, 93.1% (27 of 29) of laboratories had been inspected by the College of American Pathologists. Facility occupied bed sizes included 48.3% (14 of 29) with 300 or fewer and 51.7% (15 of 29) with more than 300. A total of 17 of 28 facilities (60.7%) had teaching programs, of which 13 (76.5%) involved pathology resident training. Overall, 72.44% (21 of 29) of institutions were in urban (city and suburban) locations and 93.1% (27 of 29) were nongovernmental.

### Performance Indicators and Testing Practices

Responses to a questionnaire about testing practices are summarized in Table 1. The performance indicator distributions as percentage of cases meeting criteria for each test reported by participants are shown in Table 2. There were no practice or demographic characteristics significantly associated with any of the performance indicators. A computerized order entry system capable of displaying results of prior testing at the time of order entry was reported as available at 40.0% (12 of 30) of laboratories. This factor was not associated with better performance for any of the 3 tests. However, specific information about how, or if, order entry systems were specifically applied to any of the 3 tests evaluated for this study was not obtained.

### Free PSA

The annual testing volume is shown in Table 3. Nineteen of 29 facilities (65.5%) referred free PSA testing to a reference laboratory. Among 583 cases in which the type of test was specified, 417 (71.5%) were free PSA alone and the remaining 166 (28.5%) involved measuring free PSA as part

Test	No.	All Institutions Percentiles				
		10th	25th	50th (Median)	75th	90th
Free PSA	29	119	1198	2650	8095	20 753
Anti-HAV	27	21	46	377	1067	1584
FVL	29	37	62	155	280	573

Abbreviations: anti-HAV, anti-hepatitis A virus antibody; FVL, factor V Leiden; PSA, prostate-specific antigen.

of the PHI test. The distribution of upper and lower limits for total PSA that participants specified being used for interpretation of free PSA is shown in Table 4. A total of 790 free PSA tests, in aggregate, were reported by 28 participants.

The most common cause for not meeting testing criteria was lack of information about total PSA results within the last 90 days in 474 (60%). Among all facilities, the median percentage of such cases was 26.7%, with 16.7% to 81.7% within the 25th to 75th percentile range and 3.3% to 100% within the 10th to 90th percentile range. Among the remaining 316 free PSA testing events in which total PSA results were available within 90 days, free PSA was performed in 153 (48.4%) for which prior total PSA results were outside the laboratory's range for reliably interpreting free PSA results. Among these 153 cases, prior total PSA results were lower than 0.5 ng/mL in 51 (33.3%) and higher than 20 ng/mL in 19 (12.4%). Overall, 163 of all 790 free PSA tests (15.2%) met the study's criteria for appropriate utilization, although performance ranged widely among participants (Table 2). If instead a fixed range for total PSA of 4.0 to 10.0 ng/mL had been putatively used, 144 cases (18.2%) would have met criteria for appropriate testing.

Only 1 of 28 participants (3.6%) reported routinely checking the patients' total PSA levels before processing orders for free PSA. However, total PSA was not performed within 90 days of testing free PSA in 26 of 30 cases (86.7%) for this participant, and total PSA for 2 of the 4 remaining cases was outside the appropriate range for interpretation of results. Utilization criteria were more often met for free PSA alone (137 of 417; 32.9%) compared with when free PSA was used as part of the PHI test (26 of 166; 15.7%);  $\chi^2$  test,  $P < .001$ . There were no other practice or demographic factors significantly associated with free PSA utilization performance.

#### Total Anti-HAV

The annual testing volume for anti-HAV is shown in Table 3. Fourteen of 26 facilities (53.8%) referred anti-HAV testing to a reference laboratory. The anti-HAV testing was repeated on 8.5% (60 of 709) of patients who had previously tested positive for anti-HAV antibodies during the previous 3 years. Within this group, 56 patients had 1 previous positive test and 4 had positive results from 2 previous testing episodes. Among all facilities, the distribution of anti-HAV tests meeting criteria is shown in Table 2. Only 1 of 28 participants (3.6%) reported routinely checking for prior anti-HAV results before processing new anti-HAV orders. Performance for this participant ranked at the 75th-percentile range, with 29 of 30 cases (96.7%) meeting criteria.

Anti-hepatitis A virus antibody was included as a component of 1 or more viral hepatitis testing panels by 9

PSA, ng/mL	No. (%)
Lower range limit	
0.0	6 (20.7)
0.1	1 (3.4)
2.0	1 (3.4)
2.5	2 (6.9)
2.6	2 (6.9)
4.0	17 (58.6)
Upper range limit	
4.0	5 (17.2)
6.5	1 (3.4)
10.0	22 (75.9)
99.0	1 (3.4)

of 27 laboratories (33.3%), all of which included immunoglobulin M (IgM)-specific anti-HAV in at least 1 of the panels. There was no association between utilization performance and inclusion of anti-HAV in a test panel.

#### Factor V Leiden

The annual testing volume for FVL is shown in Table 3. Seventeen of 29 facilities (58.6%) referred FVL testing to a reference laboratory. Factor V Leiden tests were repeated on 4.8% (40 of 839) of patients who had been previously tested for the same mutation during the previous 3 years. Within this group, 35 had been tested once before and 5 patients twice. None of the repeat test results were discordant (ie, presence/absence of mutation, different mutation).

Among all facilities, the distribution of FVL tests meeting utilization criteria is shown in Table 2. Six of 29 study participants (20.7%) reported that orders for FVL mutation testing were automatically screened for prior testing before processing. However, this practice was not significantly associated with better performance, and 4 of these 6 participants reported duplicate testing in 1 or more cases. In addition, 41.4% (12 of 29) of participants reported that they would cancel or defer FVL mutation testing if results from prior testing were documented.

#### DISCUSSION

This study evaluated the utilization of FVL, anti-HAV, and free PSA tests based on criteria that involved checking earlier results, if available, as a precondition for testing. Performance, as measured by meeting appropriate testing criteria, was poorest and most variable for free PSA compared with the other 2 tests. There were no associations found between utilization performance and test volume or practice demographics (eg, bed size, teaching status), although the total number of participants was relatively small, as was the overall variability in performance between laboratories for anti-HAV and FVL. Little utilization review of these tests was reported, except for FVL, in which about 40% of participants had some type of screening process. This factor was not associated with better performance, perhaps because of the small number of FVL tests evaluated and low frequency of repeat FVL tests. Furthermore, only a partial number of utilization practices were evaluated for the



3 tests examined (Table 2), which also limited the ability to fully evaluate potential causes for unnecessary testing.

### Free PSA

Measurement of free PSA alone or as part of the PHI test provides more specificity than total PSA for assessing the likelihood of prostate cancer.<sup>7,8</sup> Cancer risk is inversely related to the percentage of free PSA in serum. Similarly, the PHI incorporates both free PSA and proPSA (the cancer-associated form of free PSA) to calculate a score that is directly associated with risk. However, use of free PSA for prostate risk assessment is not valid when total PSA is outside an interpretable range established by the testing laboratory. This range is typically 4.0 to 10.0 ng/mL, although an alternative lower limit of 2.0 to 2.5 ng/mL has been suggested. Furthermore, the PHI test is US Food and Drug Administration–approved for use only when the total PSA is between 4.0 and 10.0 ng/mL.

Some participants reported using 0.0 to 4.0 ng/mL as the total PSA range for interpreting free PSA, which is the typical reference range applied for interpreting total PSA alone. It is possible that these participants either misunderstood the question or were not aware that free PSA required a specific total PSA range for interpretation. Nevertheless, using fixed criteria (4.0–10.0 ng/mL) as the total PSA interpretable range instead of that assigned by the specific laboratories would not have substantially affected performance. Only 1 facility reported having a procedure for checking total PSA prior to testing free PSA, and this factor did not affect performance. Although 90 days may have been too little time to allow for previous total PSA test results to be considered as a condition for free PSA testing, about half of free PSA tests were still inappropriately performed when prior results were available within this time frame. In addition, total PSA was well below (<0.5 ng/mL) or above (>20 ng/mL) levels in many cases for which free PSA testing would not be indicated under any circumstance. Thus, lack of systems for prerequisite checks likely contributed to the overall poor performance in which appropriate conditions for free PSA testing were frequently not met.

About two-thirds of participants reported referring free PSA testing to a reference laboratory. This indicates that some reference laboratories are likewise reporting results that lack interpretive value. One study<sup>9</sup> involving 40 618 free PSA tests performed by a national reference laboratory reported that 38% were done when total PSA was outside the 2.5 to 10.0 ng/mL range and 19% when total PSA was below 1.0 or above 15.0 ng/mL. These results are comparable with those from this Q-Probes study in which 48.4% of free PSA tests were performed when total PSA was outside the laboratory's interpretable range and 54.4% when total PSA was outside the 4.0 to 10.0 ng/mL range.

Free PSA utilization could be improved by developing reflex testing protocols based on prerequisite total PSA results or by automatically suppressing free PSA results if total PSA is outside the interpretable range. For example, one study involving 28 facilities and 5791 free PSA results reported 38.8% were done when total PSA was outside the 4.0 to 10.0 ng/mL range and 6.7% were done when total PSA was lower than 0.5 ng/mL or higher than 25 ng/mL. However, 7 of 28 laboratories (25%) in this study had practices in place for canceling free PSA orders based on total PSA results. Free PSA was appropriately tested in 91.6% of cases in this subgroup compared with 51.2% for

the remaining laboratories without utilization review and test cancellation procedures.<sup>10</sup>

The results from this Q-Probes study as well as previous studies indicate that inappropriate free PSA testing may be widespread because of lack of effective utilization review practices. This not only leads to unnecessary, wasteful testing, but more importantly, it increases the risk that results might be misinterpreted and potentially lead to diagnostic errors. For example, a low percentage of free PSA might be misinterpreted as high risk for prostate cancer if the patient's total PSA is too low for meaningful analysis of results. Laboratories can significantly improve the utilization of free PSA testing by establishing protocols and criteria for reflexive free PSA testing either on site or in collaboration with their reference laboratory.

### Total Anti-HAV

Total anti-HAV antibody testing is performed to document the immune status of adults prior to vaccine administration or to detect past infection. Anti-hepatitis A virus antibodies persist for life. Therefore, repeat testing when prior results are positive has no diagnostic benefit. The results from this study indicate that unnecessary anti-HAV antibody testing was performed to some degree by most facilities. Furthermore, a larger number of cases might have been identified if the look-back period had been extended beyond 3 years.

Because anti-HAV antibody is typically an automated and relatively inexpensive test, the cost of reviewing cases to prevent a small proportion of redundant orders may exceed the benefits unless it can be done efficiently. Therefore, utilization review might be practical only if managed by information systems with access to archival information and rule-based alerts that could automatically notify health care providers about prior diagnostic test results or automatically cancel orders before or after accessioning if a specimen had already been collected. Although these systems are not yet widely available, this study shows their potential value.

Among 27 participants, 9 (33.3%) reported using hepatitis panels that included combined testing for both total and IgM-specific anti-HAV antibody tests. Measuring IgM anti-HAV is indicated for suspected acute hepatitis A infection. However, performing both tests together on a panel would be redundant and unnecessary if results of total anti-HAV, if tested first, were negative. For those cases, nonreactive total anti-HAV would exclude both acute and past infection, as well as vaccination. Thus, additional testing for IgM anti-HAV would have no additional value.<sup>11</sup> This finding serves as an example of how panel configuration might unintentionally lead to indiscriminate overtesting.<sup>12</sup> Contributing factors might involve absence of effective systems to apply reflex testing or failure to recognize that testing total and IgM-specific anti-HAV together rather than in sequence is wasteful. Although there was no association between inappropriate retesting rates and the presence of anti-HAV tests on hepatitis panels, laboratories that experience higher rates of redundant anti-HAV testing among patients who previously tested positive should investigate if panel configuration is contributing to overutilization.

Finally, with widespread vaccination of children and high-risk adults, the incidence of HAV infection has declined more than 95% since a vaccine became available in 1995.<sup>13</sup> In 2014, the Centers for Disease Control and Prevention<sup>14</sup> estimated an incidence of 2500 new HAV infections occurred in the United States, many associated with

outbreaks. Therefore, targeted testing may offer more value than using total anti-HAV alone or combined with IgM-specific antibody either as part of routine viral hepatitis testing or included in general viral hepatitis panels.

### Factor V Leiden

Factor V Leiden mutation is the most common genetic abnormality associated with thrombophilia, occurring in about 5% of white Americans. Testing for the mutation or phenotypic expression by activated protein C resistance testing is recommended for evaluating patients, especially those younger than 50 years who have any venous thrombotic event, patients with a strong family history of thrombosis, female smokers who have had a myocardial infarction, and women with recurrent pregnancy loss or unexplained complications (eg, severe preeclampsia).<sup>15</sup> Widespread screening is not recommended.

Although guidelines for establishing appropriate testing intervals for common laboratory tests have been developed for some tests and disorders,<sup>16</sup> repetitive testing is highly variable and largely dependent on practice preferences as well as configuration of test ordering systems. Testing for genetic mutations or phenotypes is an exception. In these cases, repeat testing for the identical mutation or phenotype is rarely indicated because the outcome is expected to be the same. The American College of Medical Genetic and Genomics, as part of the Choosing Wisely initiative by the American Board of Internal Medicine,<sup>17</sup> recommends against ordering a duplicate genetic test for inherited conditions unless there is uncertainty about the validity of the existing test result, such as, for example, concern about sample mislabeling, clerical errors, or analytical problems.

Among participants in this Q-Probes study, FVL was retested in 4.8% (40 of 839) of cases. This percentage might have been higher if the look-back period had extended past 3 years. One study<sup>18</sup> from a single academic medical center reported that the incidence of duplicate genetic testing was 3.3% for thiopurine methyltransferase genotype, 0.3% for hemochromatosis gene mutation, and 0.9% for CYP450 2D6 mutations. These rates were lower than observed in this Q-Probes study, which involved a different genetic test and more facilities. Another study that actively reviewed redundant genetic tests reported canceling 99 orders, of which 59 involved FVL and 20 involved hemochromatosis gene mutations.<sup>5</sup> Thus, duplicate genetic testing may be relatively common and could justify active review and intervention for some of the more frequently ordered tests.

Utilization review by participants was more common for FVL than for the other tests. This review included checking for previous results before processing a new order. Furthermore, many participants reported that they would cancel or defer FVL testing if prior results had been documented. This may be due to the higher relative cost of a molecular-based assay compared with the other tests (free PSA and anti-HAV) evaluated. Moreover, canceling an order for an identical genetic or phenotypic test may be less clinically provocative as compared with questioning or canceling other types of laboratory orders. Besides reducing unnecessary testing, reporting previous FVL results identified by utilization review would provide more rapid information for patient management by reducing the time required to obtain the same result by testing. This presumes that the health care practitioner is not aware of prior FVL results at the time an FVL test was ordered and does not intend to retest the patient for the same mutation.

Information about methods used for utilization review was not obtained. Manual review of orders is not practical but may be effective for lower-volume and higher-cost tests.<sup>19</sup> Utilization of FVL testing could also be improved through the use of clinical decision support systems that automatically check for previous test results during the ordering process.<sup>6</sup> In this study, 12 of 30 participants (40%) reported using order entry systems that could display results of prior testing at the time or order entry. However, information about use of these systems for ordering FVL was not collected. Until automated utilization review and decision support applications are more widely embedded into health information systems with evidence-based utilization criteria, significant reductions in unnecessary and inappropriate testing will remain difficult to achieve. Even when available, these systems may still have limitations because of problems with continuity of health care, universal patient identifiers, genetic test nomenclature, and lack of interoperability among health information systems.<sup>20–22</sup> For example, one study involving a large health care system with a consolidated health information system reported that 30% of repeat FVL tests initially involved a different facility.<sup>23</sup>

### SUMMARY

Although the need to improve test utilization has been recognized for decades,<sup>24</sup> value-based incentives and growing attention toward improving outcomes and reducing diagnostic errors are factors that may drive stronger integration of utilization management with laboratory quality systems.<sup>2,19,25</sup> Results from this Q-Probes study highlight examples of utilization management improvement opportunities aimed at reducing waste, and, in the case of free PSA testing, preventing misinterpretation of results. Future laboratory quality improvement priorities should include the development of robust clinical decision support systems that are driven by evidence-based testing criteria. Finally, greater awareness of and support for utilization stewardship will advance the value of laboratory medicine.

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