COLLEGE of AMERICAN PATHOLOGISTS

Free Prostate Specific Antigen (PSA)

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SYNOPSIS AND RELEVANCE

Testing of free prostate-specific antigen (PSA) can be useful in discriminating prostate cancer from prostatic hyperplasia when used in the proper situations. This module will:
1. Educate healthcare providers about the use of free PSA testing for assessing prostate cancer risk.
2. Describe reflex testing and algorithms to improve free PSA ordering practices.
3. Impact patient care by ensuring that free PSA results are properly tested and interpreted to reduce risk of diagnostic errors.

OBJECTIVES

1. Optimize measurement of free PSA as well as its use in the prostate health index (PHI) based on results from prerequisite testing for total PSA to avoid potential misinterpretation of results.
2. Limit measurement of free PSA or PHI based on results from prerequisite testing for total PSA in order to reduce unnecessary testing.

BACKGROUND

PSA circulates through the body bound to other proteins or unbound. The free PSA test measures the amount of unbound PSA, whereas routine tests for PSA measure both free and bound PSA or “total” amounts of PSA. PSA levels can be elevated in prostate cancer and in a variety of benign conditions including prostatitis, prostate hypertrophy, and advanced age. Until recently, biopsy was recommended when total PSA exceeded 4.0 ng/mL. However, this approach results in a high number of unnecessary biopsies of patients with inflammation or benign enlargement of the prostate. For unclear reasons, patients with cancer make less free PSA than patients with benign prostate conditions and the percentage of free PSA can better estimate the likelihood a biopsy will show cancer than the total PSA alone. Thus, free PSA testing may help determine which patients to recommend for prostate biopsy when the total PSA level is mildly elevated (eg, 4.0-10.0 ng/mL).

Measurement of free prostate-specific antigen or its use in the prostate health index (PHI) may be indicated when total PSA levels fall within the defined range, also known as the “grey area,” of 4.0-10.0 ng/mL. Lower level limits used in some facilities may be as low as 2.0 ng/mL. Other ranges above and/or below this range may be utilized by some laboratories, although United States Food and Drug Administration has only approved the PHI test for use when total PSA is 4-10 ng/mL. Under these circumstances, free PSA or PHI may provide more sensitivity than total PSA for assessing risk and the likelihood of detecting prostate cancer on biopsy. The probability of prostate cancer is inversely related to the percentage of free PSA in serum while PHI is directly related to cancer risk, but only when total PSA is within the defined range (typically 4.0 to 10.0 ng/mL).

Outside of the defined range, free PSA and PHI cannot be reliably interpreted and have no value for patient assessment or management, and could even be misinterpreted. It is well documented that free PSA is still often performed even when total PSA falls outside the defined range for which the proportion of free PSA or PHI can be evaluated. This could be due to lack of knowledge about importance of total PSA as precondition for free PSA testing or lack of effective means for checking for and averting mis-orders.

INTERVENTIONS

Results of total PSA can serve as a prerequisite for determining if further testing for free PSA or PHI would be of value to avoid unnecessary testing and misinterpretation of free PSA results. Some approaches for appropriate testing are described here.

1. Develop a reflex testing strategy for free PSA and/or PHI based on initial evaluation of total PSA. This may depend on how and where testing is performed. An example is illustrated in Appendix B.
   a. Free PSA testing is performed on site
      i. Perform both total PSA and free PSA but only report free PSA if total PSA is within the defined range.
      ii. Perform total PSA first and reflex to measure and report free PSA when total PSA is within the defined range, otherwise do not test or report free PSA results.
   b. Free PSA testing is performed by a reference laboratory, but total PSA is done on site
      i. Perform total PSA on site and send free PSA to reference laboratory only if total PSA is within the defined range.
      ii. Establish a PSA panel with the reference laboratory to test and report free PSA results only if total PSA is within the defined range.
   c. Free PSA and total PSA are performed by a reference laboratory
      i. Establish a free PSA panel with the reference laboratory to test total PSA first and test (or report) free PSA only if the total PSA is within interpretable range.
2. Explain the total PSA and free PSA strategy to stakeholders and describe the rationale to gain support for changing free PSA testing protocols.
3. When a free PSA is not performed and/or reported due to the initial evaluation of total PSA results, consider adding a comment about why the free PSA or PHI test would lack interpretable results, and would not be of diagnostic value.

INTERVENTION ANALYSIS

Assessing the use of free PSA is straightforward (Appendix A):

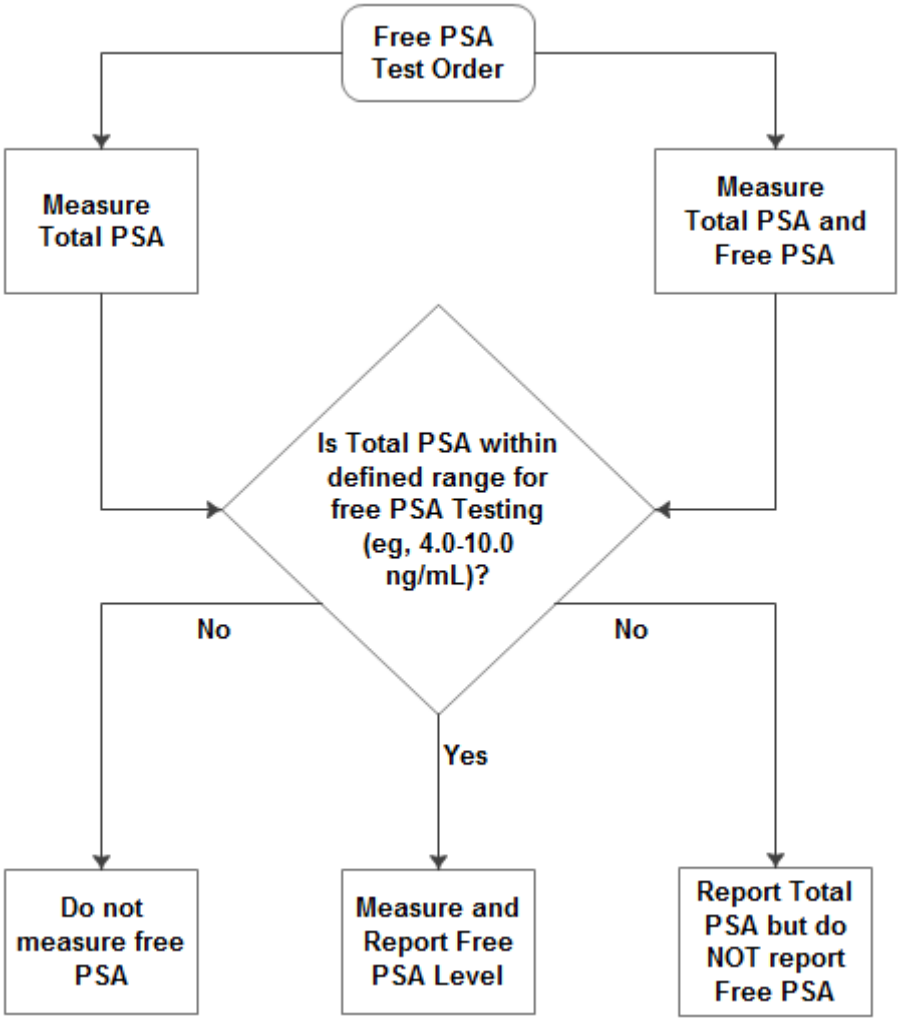
1. Review the procedure for free PSA or PHI, and interpretive reference ranges, either established by the laboratory if done on site, or by the reference laboratory if the specimens are sent to a reference laboratory for testing. The range of total PSA values for which the percent of free PSA or PHI can be interpreted should be specified.
2. Retrospectively, choose a specified period (eg, prior 3 months) and review previously ordered total PSAs, free PSAs, and/or PHI tests to determine the following:
   a. Determine the total number of free PSA/PHI tests performed.
   b. Determine the total number of free PSA test results reported when the total PSA was within the defined range.
   c. Determine the total number of free PSA test results reported when the total PSA was outside the defined range.
   d. Calculate the percent of appropriate free PSA test reporting.
3. After implementing free PSA test improvement interventions, recheck the number of cases in which free PSA is reported due to total PSA results that are outside the defined range by repeating the actions in Step 2 above using the same time period length. See Appendix A for calculating the impact of changes in free PSA testing.
   a. Determine the total number of free PSA/PHI tests performed.
   b. Determine the total number of free PSA tests results reported when the total PSA was within the defined range.
   c. Determine the total number of free PSA test results reported when the total PSA was outside the defined range.
   d. Calculate the percent of appropriate free PSA test reporting.
   e. Calculate the percent change in appropriate free PSA test reporting before and after intervention.

APPENDIX A: METHODS TO ASSESS INTERVENTION IMPACT

Pre Intervention; in a specified time period	
Total number of free PSA/PHI tests performed	A1
Total number of free PSA/PHI test results reported when total PSA was within the defined range	A2
Total number of free PSA done when total PSA was outside the defined range	A1-A2 = A3
Percent of appropriate free PSA test reporting	A2/A1 x 100% = A4%

Post Intervention	
Total number of free PSA/PHI tests performed	B1
Total number of free PSA/PHI test results reported when total PSA was within the defined range	B2
Total number of free PSA done when total PSA was outside the defined range	B1-B2 = B3
Percent of appropriate free PSA test reporting	B2/B1 x 100% = B4
Percent change in appropriate free PSA test reporting post intervention	A4%-B4% = C1%

APPENDIX B: SAMPLE ALGORITHM FOR FREE PSA TESTING



QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE

Understand that free PSA can only be interpreted or is of value if total PSA is within specific range, typically 4-10 ng/mL.

Free PSA % and Risk of Prostate Cancer			
Free PSA %	**50-59 years**	**60-69 years**	**>69 years**
<10%	49.2%	57.5%	64.5%
10-18%	26.9%	33.9%	40.8%
18-25%	18.3%	23.9%	29.7%
>25%	9.1%	12.2%	15.8%

QUESTION 1

A 49-year-old male with total PSA of 1.9 ng/mL and normal digital rectal exam requests free PSA measurement because he read that the test is more specific for prostate cancer. In this case free PSA testing is not indicated because:

A. Patient is too young.
B. Patient should first have prostate biopsy.
C. Prostate health index is the preferred test.
D. There is no evidence that total PSA is rising.
E. Total PSA is too low.

The correct answer is E. Free PSA cannot be interpreted when total PSA is at 1.9 ng/mL.
A is incorrect. Age (49 years old) affects interpretation but is not an indication for free PSA testing.
B is incorrect. Biopsy is not indicated with a normal digital rectal exam.
C. is incorrect. In this case, the prostate health index would have no greater value than free PSA.
D. is incorrect. A rising total serum PSA concentration (velocity) is not necessary to justify free PSA testing.

REFERENCE

Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC. Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. *J Gen Intern Med*. 2000;15:739–748.

QUESTION 2 OBJECTIVE

Understand that free PSA has no value for assessment of prostate cancer risk when total PSA is elevated.

QUESTION 2

A 55-year-old male has the following history for PSA testing:

Date	Total PSA (ng/mL)	Free PSA
02/04/2016	15.4	26.1%
01/18/2017	19.9	28.0%
04/09/2018	31.1	29.9%

Which of the following statements is correct?

A. Rise in total PSA is not clinically important when % free PSA is also rising.
B. In this case, total PSA is more specific for cancer than free PSA.
C. Prostate health index should be performed due to unusually high free PSA percentage.
D. Risk of prostate cancer is less than 10% because free PSA is >25%.
E. Risk of prostate cancer is low due to rising free PSA values.

The correct answer is B, since total PSA is elevated (>10.0 ng/mL) free PSA cannot be interpreted. As a result, only total PSA and change over time (velocity) is of value for assessing prostate cancer risk.

A is incorrect. Free PSA cannot be accurately interpreted at these high total PSA levels and rise in total PSA is more clinically significant than free PSA for predicting risk of prostate cancer.
C is incorrect. In this case, the prostate health index would have no greater value than free PSA.
D is incorrect. In this case free PSA has no value for assessing prostate cancer risk.
E is incorrect. In this case relative change in free PSA has no predictive value for risk of prostate cancer.

REFERENCES

1. Vickers AJ, Till C, Tangen CM, Lilja H, Thompson IM. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. *J Natl Cancer Inst.* 2011;103(6):462-469.
2. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA.* 2014;311(11):1143-1149.

QUESTION 3 OBJECTIVE

Understand that use of a free PSA panel can improve how the test is ordered (ie, to measure free PSA only when total PSA is within interpretable range).

QUESTION 3

The most important reason to use a free PSA test panel is to:

A. Account for age-related reference ranges.
B. Help meet current PSA screening guidelines.
C. Increase the sensitivity of total PSA for prostate cancer risk.
D. Reduce the risk of misinterpreting results.
E. Simplify free PSA ordering.

The correct answer is D. Use of a reflex panel in which total PSA is measured first and the results are used to determine if free PSA should be tested will avoid misinterpretation of results when total PSA is outside the range in which the proportion in the free form can be reliably used to predict cancer risk.
A is incorrect. Use of a free PSA reflex panel has no impact on age-related interpretation of free PSA test results.
B is incorrect. Use of a free PSA reflex panel would not help meet PSA screening guidelines.
C is incorrect. Use of a free PSA reflex panel would have no impact on how sensitive total PSA is for predicting risk of prostate cancer.
E is incorrect. Use of a free PSA reflex panel is not intended to simplify the ordering of free PSA.

REFERENCES

1. Jackson BR, Roberts WL. Brief report: Free prostate-specific antigen test utilization. Consistency with guidelines. *J Gen Intern Med.* 2005;20(9):859-861.
2. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen–based prostate cancer screening strategies: model estimates of potential benefits and harms. *Ann Intern Med.* 2013;158(3):145-153.

MODULE REFERENCES

1. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen–based prostate cancer screening strategies: model estimates of potential benefits and harms. *Ann Intern Med.* 2013;158(3):145-153.
2. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA.* 2014;311(11):1143-1149.
3. Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC. Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. *J Gen Intern Med*. 2000;15:739–748.
4. Jackson BR, Roberts WL. Brief report: Free prostate-specific antigen test utilization. Consistency with guidelines. *J Gen Intern Med.* 2005; 20(9):859-861.
5. Vickers AJ, Till C, Tangen CM, Lilja H, Thompson IM. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. *J Natl Cancer Inst.* 2011;103(6):462-469.
6. Javan B, Zlotta A, Remzi M et al. Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. *J Urol.* 2000;163(4):1144-1148.
7. Faria EF, Carvalhal GF, dos Reis RB et al. Use of low free to total PSA ratio in prostate cancer screening: detection rates, clinical and pathological findings in Brazilian men with serum PSA levels <4.0 ng/mL. *BJU Int*. 2012;110(11 Pt B):E653-E657. doi: 10.1111/j.1464-410X.2012.11398
8. Haese A, Dworschack RT, Partin AW. Percent free prostate specific antigen in the total prostate specific antigen 2 to 4 ng./ml. range does not substantially increase the number of biopsies needed to detect clinically significant prostate cancer compared to the 4 to 10 ng./ml. range. *J Urol.* 2002;168(2**)**:504-508.https://doi.org/10.1016/S0022-5347(05)64668-X