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SPECIALISED MEDICAL PATHOLOGY

[-2]proPSA and *phi* in prostate cancer

THE PATHOLOGIST'S MEMORANDUM

BIOPATHOLOGY

The *phi*, or *Prostate Health Index*, is an index based on the measurement of a new serum marker for prostate cancer, known as [-2]proPSA. [-2]proPSA is an isoform of PSA, which is almost exclusively expressed by prostate cancer cells (which is not the case for total PSA). The combination of total PSA and free PSA in the *phi* calculation gives rise to a considerable improvement in detection specificity of prostate cancer, and as such, significantly reduces the need to perform biopsies.

Prostate cancer is suspected when confronted with clinical symptoms, the detection of an anomaly upon digital rectal examination or an increase in serum levels of total PSA. Definitive diagnosis is made through the use of anatomical pathology investigations, which are performed on biopsy samples collected with ultrasound guidance. A total PSA concentration between 0 and 4 ng/mL does not exclude prostate cancer and a concentration between 4 and 10 ng/mL does not enable the differentiation between benign prostrate hypertrophy and prostate cancer.

- **The *phi* index improves the detection of prostate cancer and better targets the biopsy indications:** the higher the *phi* index is, the greater the risk of having prostate cancer.

  The *phi* index is of particular interest within two different value zones of total PSA:

  - **Total PSA values of ‹ 4 ng/mL in patients with a negative digital rectal examination result:** we know that cancers can be diagnosed in this situation. The *phi* index can be the only raised marker and several months before the diagnosis of prostate cancer is made.
  - **Intermediate values, found during the course of a benign pathology** (benign prostate hypertrophy, prostatitis) where the total PSA is "falsely positive" and leads to a large number of biopsies being taken that are unnecessary as the result is negative. In these situations, the *phi* index helps to decide whether to take a prostate biopsy or not.

- **The *phi* index detects potentially aggressive cancers**

Several studies have highlighted a significant correlation between *phi* and the Gleason score.

- **The clinical interest of *phi* compared to PCA3 or a combination of both**

PCA3 is a more specific genetic marker of prostate cancer than PSA because it is only produced by prostate cancer cells and is not influenced by the volume of the prostate. Its first indication is as a decision-making tool whether to take a second biopsy in male patients who had a negative initial biopsy result, but where cancer is still suspected. The interest of *phi*, PCA3 and their combination is currently the subject of numerous studies. Certain studies put forward that *phi* has a better performance with regards to the making the decision to take an initial biopsy, and PCA3 for subsequent biopsies. One must be rigorous with the use of these study results, which have been obtained in well-defined populations (clinical, initial biopsy or subsequent biopsies, total PSA, family history of the disease etc.), and sometimes with multi-parameter analysis.

INDICATIONS FOR TESTING

In patients aged 50 years and over, with a total PSA serum concentration between 2 and 10 ng/mL (Standard Hybritech) and a digital rectal examination that is not suggestive of disease:

- identification of a non-invasive method for patients with a highly likely of having a positive prostate

biopsy result: [-2]proPSA performs better than total PSA and the *phi* index improves the performance of [-2]proPSA alone;

- To detect potentially aggressive cancers (significant correlation between *phi*/Gleason);
- Potential interest of the *phi* index in the monitoring of patients.

ASSAY TECHNIQUE

Chemiluminescence (calibration Hybritech®) on the Access® analyser by Beckman Coulter.

INTERPRETATION for this assay

To calculate the *phi* index, [-2]proPSA, free PSA and total PSA must be measured using the same technique, a technique which does not authorise the integration of a transferred free PSA and total PSA result.

Phi index values (Hybritech calibration)	Probability of cancer (95% specificity)
0 – 21	8.4 % (1.9 – 16.1 %)
21 – 40	21.0 % (17.3 – 24.6 %)
› 40	44.0 % (36.0 – 52.9 %)

SAMPLE REQUIREMENTS

The sample conditions are the same as those for free PSA and total PSA. The sample must be collected a while after any prostate manipulation such as the digital rectal examination, prostate massage, a transrectal ultrasound or prostate biopsy.
Collect a serum sample: 1 mL is required, the minimal acceptable volume is: 700 µL. **The serum sample must be separated from blood cells within 3 hours of sample collection and then frozen.**

CONTACT DETAILS

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BIBLIOGRAPHY

1. Mikolajczyk SD, et al. A Truncated precursor form of prostate-specific antigen is a more specific serum marker of prostate cancer. Cancer Res 2001; 61: 6958–6963,

2. Sokoll LJ, SandaMG,Feng Z, et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network Study of [-2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. Cancer Epidemiol Biomarkers Prev 2010;19:1193–200.

3. Jansen FH, Van Schaik RHN, Kurstjens J, et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. Eur Urol 2010;57:921–7.

4. Catalona W. J et al. A multicenter study of -2 proPSA combined with PSA and free PSA for Pca detection in 2 to 10 ng/ml PSA range. J Urol 2011; 185:1650-1655.

5. Houlgatte A. et al. Place du [-2]proPSA et de l'index *phi* dans la détection précoce du cancer de prostate : évaluation sur une série de 452 patients Progres en urologie 2012; 22 : 279-283

6. Stephan C, et al. phi using [-2]proPSA improves detection of prostate cancer preferentially identifying aggressive cancers Clin Chem Acta 2013; 59:1, 306-314.

7. Stephan C, et al. Comparative Assessment of Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG – Gene Fusion with the serum [-2]proPSA - Based *phi* for Detection of Prostate. Cancer Clin Chem 2013; 59:1,280-288.

8. Lazzeri M, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study. Eur Urol. 2013;63(6):986-94.

9. Scattoni V, et al. Head to Head comparison of phi and PCA3 for predicting cancer at initial or repeat biopsy. The Journal of Urology 2013;190(Issue 2) : 496-501.

10. Ferro M, et al. *phi* and PCA3 significantly improve PCa detection at initial biopsy in a total PSA range of 2-10 ng/ml. PLoS One 2013; 8(7):e67687.

11. Perdonà S, et al. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. Prostate 2013;73(3):227-35.

12. Stephan C, et al. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clin Chem 2013;59(1):280-8.

13. Hansen J. Initial prostate biopsy: development and internal validation of a biopsy-specific nomogram based on the prostate cancer antigen 3 assay. Eur Urol. 2013;63(2):201-9.

14. Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A. Multicenter evaluation of [-2]proprostate-specific antigen and the prostate health index for detecting prostate cancer. Clin Chem 2013; 59(1):306-14.

15. Tosoian JJ, Loeb S, Feng Z, Isharwal S, Landis P, et al. Association of [–2]proPSA with biopsy reclassification during active surveillance for prostate cancer. J Urol 2012;188: 1131–1136.