Clinical Chemistry

Serum Prostate-Specific Antigen Testing for Early Detection of Prostate Cancer: Managing the Gap between Clinical and Laboratory Practice

Article:
Simona Ferraro, Marco Bussetti, Sara Rizzardi, Federica Braga, Mauro Panteghini.
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Clin Chem 2021; 67:3 543-53. https://doi.org/10.1093/clinchem/hvaa268

Guest: Dr. Simona Ferraro is in the Clinical Pathology Unit of the Luigi Sacco University Hospital in Milan, Italy.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Clinical practice guidelines for early detection of prostate cancer recommend for clinical decision-making of personalized prostate-specific antigen-based management to improve the risk benefit ratio of the screening strategy. Some important issues regarding the PSA determination in the clinical framework are however still neglected in current guidelines and would serve to improve their effectiveness. A mini-review appearing in the April 2021 issue of *Clinical Chemistry* examined PSA testing for early detection of prostate cancer and managing the gap between clinical and laboratory practice to help address that very question.

The lead author for that paper is Dr. Simona Ferraro. She is in the Clinical Pathology Unit of the Luigi Sacco University Hospital in Milan, Italy, and she's our guest in this podcast. So, first of all, Dr. Ferraro, how have the recent updates of clinical practice guidelines addressing the early detection of prostate cancer really changed the use of PSA in the diagnostic workup of that disease?

Simona Ferraro: Well, I think that the main challenge of the redesign of the clinical practice guidelines was to enhance the benefits associated to the use of PSA in the screening context and in clinical decision making. And this was substantially made by building individualized risk-adapted approaches to screening, biopsy referral, and cancer treatment. For instance in the referral context we assisted to the shift from the use of one single PSA cut-off point to the introduction of PSA-based risk thresholds to recommend biopsy by informing patients on the probability to exclude or detect the presence of an advanced prostate cancer. And I really think it is a relevant point to account for.

Bob Barrett: So, do you think that the use of fixed cutoff values for PSA have been the primary cause for overdiagnosis, overtreatment and of the high rate of undue biopsies?

Simona Ferraro: Well we have to consider that the adoption of one single PSA cut-off point relied on an acceptable trade-off between

diagnostic sensitivity and diagnostic specificity, and that in the clinical practice it has been tolerated 1 cancer detected for every 3 performed biopsies. A large body of literature supporting the update of the recommendations has shown that the use of the conventional cut-off point, has implied a high rate of undue biopsies and has increased the rate of diagnosis and of treatment of slow growing prostate cancers. In other words it has caused overdiagnosis and overtreatment and this is well reported in the running guidelines. And so, the updated guidelines now endorse the use of PSA-based risk thresholds to maximize benefits and decrease the harms associated to biopsy and treatment. And to do this, some authoritative voices claim that PSA-based risk thresholds have to be estimated by using as outcome the detection of prostate cancer of advanced grade and not of any grade. And this is relevant to highlight because it has to be acknowledged by clinical researchers.

Bob Barrett: In your paper, you report that the inter assay variability of current PSA methods should prevent from the use of one common cutoff point for biopsy referral. Do you think that these PSA-based risk thresholds for advanced cancer should be estimated according to the method used?

Simona Ferraro: Well we have recently published a paper on Clinical Chemistry reporting about the poor state of harmonization of current PSA methods. And in the course 2006 [Carsten] Stephan on Clinical Chemistry had just reported on the poor interchangeability of PSA results obtained from different methods. However this information had to be updated since now we have available new analytical platforms, the cut-off rule has lapsed, and we have established the clinical goals for the inter-method bias according to biological variability data. In our work, we have reported that the state of harmonization of current immunoassays is still suboptimal and the inter-method bias exceeds the goal of 10.6% which is the interassay bias goal for the clinical application of PSA results. Accordingly, it is rather clear that we need to have available in the clinical practice method-dependent risk thresholds of PSA for biopsy referral. And so our next work will define PSA thresholds for identifying or excluding the presence of an advanced PCa as an aid in the personalized management of the diagnostic workup. These thresholds will be estimated from a well calibrated risk prediction model using as outcome the presence of an advanced cancer. To do this we will resort to a case series of about 900 patients who underwent biopsy and had a pre-biopsy PSA determination performed by Roche assay. Our next challenging step will be to try to convert the established PSA risk thresholds estimated by Roche assay into the corresponding concentrations assayed by the other methods. However, the evidence of a non-constant bias between methods might prevent this conversion.

Bob Barrett: Well, from your work, we perceive that the recommendations on PSA-based screening have evolved according to the results of some clinical trials, but there are no clear recommendations to aid clinicians to use PSA appropriately. What are your thoughts about this?

Simona Ferraro: Yes, this is the great gap. We have observed that recent clinical practice guidelines ignore the analytical performance of available PSA assays, and ignore that these have changed over the past two decades. Anyway several studies have reported that neglecting the analytical performances of PSA assays is one of the main causes of patient misclassification. There are several critical methodological issues that may influence the interpretation of PSA results that we have discussed in this paper. First the heterogeneity of the measurand which is further increased in patients with prostate cancer and benign prostatic inflammation with respect to other patients. Second we have discussed about the different capability of current marketed assays to recognize the various PSA forms according to their antibodies specificities. In conclusion I want to highlight that the knowledge of these analytical issues undoubtedly will address more pragmatic recommendations on PSA results interpretation. I remind that sound clinical trials contributing to update the clinical practice guidelines were affected by several methodological limitations concerning PSA determination. During the 10-15 years of the duration these trials blended PSA results dichotomized according to very different decision cutoffs, and blended PSA results obtained by different methods or by the same method using different calibrations. And this undoubtedly has contributed a considerable intra-study and inter-study variability and likely introduced a misclassification bias. However now we have new recommendations about the screening and biopsy referral, and we have new evidence on the analytical performances of PSA immunoassays and from our laboratory we have to account that "More than something has changed"!!!!

Bob Barrett: Well, traceability is an important component of laboratory medicine. Do you think that the calibration of all methods against the WHO international standard has not improved enough the inter assay equivalence of total PSA results?

Simona Ferraro: Unfortunately not and [Carsten] Stephan in his work had yet reported this evidence, concluding that the use of different assays and of a common decision threshold of 4 µg/L had a severe clinical impact on the decision of whether performing a biopsy or not. Anyway this evidence required to be updated since the analytical platforms have changed, and we retrieved information about the characteristics of antibodies used in the different immunoassays. Now We know that the majority of available immunoassays use pairs of monoclonal antibodies

selected for obtaining an equimolar response to free PSA and alpha1-antichymotrypsin-bound PSA. And this is a preliminary basic prerequisite to yield comparable results for clinical samples. However, we have to account that Siemens PSA assay employs as tracer antibody a polyclonal antibody and this may affect the equimolar response and thus it implies an overestimation of PSA values and this in particular in patients with benign prostatic hyperplasia having higher concentrations of free PSA. In general, the antibody pairs of current assays assure a balanced recognition of the different circulating PSA forms. Anyway some assays may be more sensitive to various circulating forms of PSA, including nicked forms which are far increased in patients with benign prostatic hyperplasia. Other assays may be more sensitive to some PSA homologs as human kallikrein 2 and thus these assays could overestimate PSA values in patients with advanced cancer. And thus finally an additional relevant basic prerequisite for obtaining reliable PSA estimates is the lack of cross-reactivity between the used antibodies and PSA homologs.

Bob Barrett: So, in clinical practice, what does it mean having information about the antibodies used in the assay in service?

Simona Ferraro: Well, the full knowledge of this information carries great relevance towards correctly interpreting the PSA concentrations observed in the clinical samples. And it is rather clear that samples drawn from patients with benign prostatic hyperplasia, with prostate cancer at early stages and with prostate cancer at late stages may exhibit different patterns of PSA expression and release and therefore may reflect differences in PSA form composition. And thus, it is clear that the knowledge of the sensitivity of the assay in service in our laboratory versus the different forms may be of aid to reliably select patients for biopsy referral or for predicting the risk for cancer. And this information should be shared with our clinicians.

Bob Barrett: That was Dr. Simona Ferraro from the Clinical Pathology Unit of the Luigi Sacco University Hospital in Milan, Italy. She has been our guest in this podcast on using PSA measurements for the early detection of prostate cancer and managing the gap between clinical and laboratory practice. She is a co-author of a mini review article on that topic that appears in the April 2021 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.