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Platinum Priority – Editorial and Reply from Author

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Use of Baseline Prostate-Specific Antigen Measurements to Personalize Prostate Cancer Screening

Stacy Loeb *

Department of Urology, New York University, New York, NY, USA

In this issue, Ørsted and colleagues report on 4383 Danish men from the Copenhagen City Heart Study who gave plasma samples in 1981–1983 at a median age of 58 yr [1]. Prostate-specific antigen (PSA) was later measured from the stored samples, and the relationship of these baseline PSA levels to prostate cancer (PCa) diagnosis and mortality was examined over 28 yr of follow-up. There were 170 PCa diagnoses and 94 disease-specific deaths in the cohort.

Despite the fact that PSA screening was not available in Denmark during the study period, the authors observed a significantly greater cumulative incidence of PCa diagnosis, metastasis, and death with increasing PSA. Compared to men with a baseline PSA level ≤ 1 ng/ml, they reported a 3.0-, 6.8-, 6.6-, 16-, and 57-fold increased relative risk of PCa diagnosis with baseline PSA levels of 1.01–2.0, 2.01–3.0, 3.01–4.0, 4.01–10.0, and >10 ng/ml, respectively. The corresponding relative risks for PCa mortality were 2.2, 5.1, 4.2, 7.0, and 14, respectively, for these groups.

This study adds to a growing body of evidence showing the important prognostic value of baseline PSA measurements, which were recently reviewed [2]. This finding has been consistently demonstrated in screening studies as well as in clinical populations without routine screening. This suggests that the results do not simply reflect ascertainment bias and that the baseline PSA value is truly a robust marker for PCa risk stratification.

The findings of Ørsted et al. [1] corroborate a prior study from the Malmo Preventive Project, which included 1167 Swedish men who gave blood samples at age 60 and were followed for more than two decades [3]. In that study, the median imputed PSA concentration at age 60 was 1 ng/ml. Interestingly, 90% of metastases and 95% of PCa deaths

occurred among men with a baseline PSA above the age-specific median.

The 2011 National Comprehensive Cancer Network guidelines recommend offering a baseline PSA measurement at age 40 to guide the subsequent screening protocol [4]. Specifically, annual screening is recommended for men with a baseline PSA level >1 ng/ml or other risk factors (eg, African American heritage, family history of PCa, or 5- α reductase inhibitor use), whereas men with a baseline PSA level ≤ 1 ng/ml and no other risk factors may defer additional testing for 5 yr.

This type of individualized screening protocol incorporating the initial PSA level is supported by the data from Ørsted et al. [1]. Men with a baseline PSA concentration ≤ 1 ng/ml have a substantially lower risk of PCa and aggressive disease. Because this was the case for approximately three-quarters of this population-based study, such a strategy would provide reassurance to the majority of men. In contrast, men with baseline PSA levels >1 ng/ml have a significantly higher rate of PCa diagnosis and death, such that careful follow-up is warranted. Thus the baseline PSA level can be used to help guide the screening protocol for individual patients.

It is possible that PCa screening protocols may become even more personalized in the future. For example, recent studies have examined the influence of genotype on PSA levels. Among men from the Baltimore Longitudinal Study of Aging, we showed that the risk of PCa at any given PSA level differed based on genetic factors [5]. Additional studies are necessary to determine whether genetic PSA adjustment would be cost-effective and would improve clinical outcomes.

In the meantime, total PSA concentrations continue to represent a useful predictor for the future risk of overall and

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* Department of Urology, New York University, 550 1st Avenue, VZ30 6th Floor (#612), New York, NY 10016, USA. Tel. +1 646 501 2559; Fax: +1 212 263 4549.

E-mail address: stacyloeb@gmail.com.

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life-threatening PCa [1]. Risk assessment can be further refined by considering other factors such as age, race, family history, and prostate volume along with the PSA measurement [6]. It is becoming increasingly clear that a risk-adapted strategy for PCa screening is superior to a “one size fits all” approach [7]. Future studies will help to better define the optimal combination of variables for a customized PCa screening program.

Conflicts of interest: The author has nothing to disclose.

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Platinum Priority

Reply from Authors re: Stacy Loeb. Use of Baseline Prostate-Specific Antigen Measurements to Personalize Prostate Cancer Screening. *Eur Urol* 2012;61:875–6

David D. Ørsted^{a,b}, Børge G. Nordestgaard^{a,b,c}, Gorm B. Jensen^c, Peter Schnohr^c, Stig E. Bojesen^{a,b,c,*}

^aDepartment of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Denmark; ^bFaculty of Health Sciences, University of Copenhagen, Denmark; ^cThe Copenhagen City Heart Study, Bispebjerg Hospital, Copenhagen University Hospital, Denmark

We thank Loeb for the positive and insightful editorial [1] regarding our study on prostate-specific antigen (PSA) for long-term prediction of prostate cancer (PCa) incidence and mortality [2]. We fully agree that our data strongly support the use of personalized PSA screening rather than a “one size fits all” approach.

As also pointed out by Loeb, major strengths of our study include that screening for PCa is not recommended in Denmark and that, in subanalyses, we studied the period 1981–1995, before PSA testing was available in Denmark. Thus in our study, a diagnosis of PCa was not a result of PSA-based screening but rather was based on clinical symptoms leading to further examination and subsequent diagnosis. In addition, we were able to examine the association between PSA at first date of testing and PCa mortality. These factors

add strength to the interpretation of our results by eliminating the influence of ascertainment bias, at least in 1981–1995. In this way, we could study the natural history between elevated PSA and PCa incidence and mortality.

The use of a baseline PSA measurement for personalized risk stratification is gaining support [3] and is already included in some PCa-screening recommendations [4]. Furthermore, previous results from randomized screening trials have shown that the use of screening intervals based on PSA levels allows detection of clinically significant cancers while reducing harmful effects of screening [5,6]. Our results support such a personalized approach, and we suggest that PSA levels at first date of testing can be used to stratify men into groups with different screening intervals (Fig. 1). Such a personalized screening strategy might reduce the number of unnecessary PSA measurements and, thus, the risk of overdiagnosis and treatment of latent PCa. It might also allow physicians to focus on high-risk individuals and hopefully ease the increasing unnecessary pressure on urology departments responsible for PCa patients.

Despite the common use of PSA in clinical practice worldwide, there is continued, and sometimes heated, debate regarding PSA-based screening. Recently, the US Preventive Services Task Force issued a recommendation against use of PSA for screening purposes in asymptomatic low-risk men [7]; this guidance is in line with recommendations in most European countries. However, in the past, PSA has been used differently in the United States compared to many countries in Europe. This may be due to cultural and economic factors influencing patients' and physicians' incentives to diagnose and treat PCa. A health system providing direct remuneration per service to physicians,

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* Corresponding author. Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark. Tel. +45 3868 3843; Fax: +45 3868 3311. E-mail address: stebo@heh.regionh.dk (S.E. Bojesen).