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Platinum Priority – Editorial and Reply from Authors Referring to the article published on pp. 745–752 of this issue

Early Detection of Prostate Cancer: More Information, More Clarity

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Screening for prostate cancer (PCa) is among the most controversial topics in the field of urology. The outcome of this increasingly strident debate will have considerable impact on the field in developed countries, where the detection and management of PCa constitutes a large portion of what urologists manage. Recently, the US Preventive Services Task Force (USPSTF) finalized a crisp recommendation that routine prostate-specific antigen (PSA)–based screening for PCa be stopped. This recommendation won praise from some and strong denunciation by others but left most men wondering what to do.

There is truth on both sides of the debate for and against PSA testing. PCa mortality has declined considerably—by 40%—since the advent and widespread uptake of PSA testing in the late 1980s in North America. Large, highly powered, contemporary clinical trials have confirmed the impact of PSA testing in reducing metastasis and cancer-specific mortality [1,2], and projection models have attributed as much as one-half of the observed decline in mortality to PSA screening [3]. However, many overinterpret the absolute impact of this decline for an individual man and fail to acknowledge the considerable, well-documented problems of PCa overdetection and overtreatment. The debate can be resolved only with more granular data and careful interpretation divorced from the emotional positions that can erode the *middle ground* information all men deserve.

The current article by Schröder and colleagues [4], a superb group of clinical scientists who have added much to what we know about both the risks and benefits of PSA screening, presents novel and important information about the impact of PSA testing on one very important end point: the risk of metastatic PCa, a harbinger of PCa death in most cases. The authors assessed information available for

76 813 men aged 55–69 yr from four centers of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Participants were randomized to either PSA screening every 2–4 yr or usual care. Metastatic (M+) disease was defined by positive lesion on imaging or PSA >100 ng/ml at time of diagnosis (defined as <3 mo after diagnosis) or during follow-up. Assuming that PSA higher than any given threshold denotes M+ disease is debatable, but the value selected is reasonable and is clearly associated with the M+ disease in the majority of cases. Participants' disease risk was stratified using conventional descriptors.

At a median follow-up of 12 yr, the rate ratio of M+ disease in the screening group compared with the control group was 0.70, which translates to a relative risk reduction of 30% and an absolute risk reduction of 3.1 lives saved within 12 yr per 1000 men. These results were based on the primary intent-to-screen analysis; in analysis adjusting for nonscreening in the intervention arm (but not for contamination with screening in the control arm), a relative risk reduction of 42% was noted for those men actually screened. Additionally, a 55.6% higher incidence of PCa was found in the screening group. The number needed to invite to screening to avert one case of M+ disease was 328, and the number needed to diagnose (NND) but not necessarily treat was 12.

However, this study notably demonstrates that the impact of screening on the risk of M+ disease is primarily seen at or shortly after diagnosis but attenuates during follow-up. The relative risk reduction at diagnosis was 50% but fell to 30% overall after accounting for the follow-up M+ cases. The authors suggested this finding may be due to increasing rates of M+ disease identified in those screened after 7-yr follow-up. In fact, the rate of M+ disease was

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How are we to interpret such remarkable findings? First, the follow-up results are a very good example of lead-time bias: PSA enables earlier detection of disease, but there is no effect on the outcome. Second, rates of both metastasis and cancer-specific mortality in both groups are certain to increase further with additional follow-up and may favor screening to a greater extent. Third, consideration of the differing times of enrollment between screening and control arms is necessary for accurate interpret duration of follow-up. Fourth, the impact of primary treatment on outcome was not assessed. The authors report that a higher rate of radiotherapy was undertaken by those who later developed M+ disease compared with those without M+ disease (45.7% vs 26.4%). It is known that in certain risk groups, different treatments may have a significant effect on outcome [6,7]. Given the authors' longstanding commitment to reevaluation of their data, it is certain that further analyses will address the last two issues.

Although the authors found differing degrees in the benefit of screening on the occurrence of M+ disease at diagnosis versus during follow-up, an explanation remains largely unexplored. For one, the age of participants at first screening ranged from 55 to 69 yr. Many advocate that screening should be initiated earlier, such as before age 50. Many have noted that a baseline PSA level in a man's 40s is a strong predictor of the future risk of PCa and, importantly, the risk of advanced disease [8,9]. Furthermore, the benefits in published screening trials suggest a direct relationship with younger participants [1,2]. However, it must be acknowledged that such earlier testing may be subject to the same lead-time bias likely noted in the current study. In addition, the current study relied largely on PSA testing alone. The use of risk calculators may better quantitate individual risk for PCa (including the risk of high-grade disease) and inform patients about the advisability of biopsy in their case. However, such calculators require validation within appropriate patient populations [10]. Furthermore, future efforts are likely to focus on a suite of efficient and effective risk assessment tools/markers (eg, demographic, genetic, clinical) focused on detection of significant PCa. Such efforts should be combined with new decision-support tools, which would better inform

individual men, in the clinical setting, of the risks and benefits of PCa early detection efforts.

With additional follow-up, the implications of M+ diagnosis, particularly in follow-up, may change, although it is unlikely that this would have affected the results of this paper. Until recently, only one therapeutic agent was available to extend life for men with castrate-resistant disease. The armamentarium has now grown to five and is rapidly expanding, and some of these novel expensive agents are approved *only* for M+ disease. Thus there is new pressure to identify M+ disease earlier in follow-up through use of more intense imaging. It is quite likely that between a stage migration within M+ and the availability of multiple effective therapies, the prognosis for men with M+ disease will improve substantially as the ERSPC and other trials continue follow-up.

So what are the take-home messages about PSA testing for the early detection of PCa today? This update from the ERPSC trial [4] has yielded the strongest evidence yet that PSA-based screening substantially reduces the incidence of metastatic PCa. The preponderance of evidence now suggests that PCa screening saves thousands of lives. However, it does so at the considerable risk of overdetection. We should not overinterpret the benefits and cannot dismiss the risks (ie, economic and personal risks of overtreatment). The facile conclusion against PSA testing by the USPSTF indicates deeply troubling overconfidence in the immutability of their weighting of relative risks and benefits of screening. Nonetheless, counseling men about the risk of overdetection before biopsy is necessary. We need to screen smarter, with baseline testing early, less intensive assessment for those at low risk, and more careful assessment of those at high risk [11]. Using risk calculators when they have been validated in a population of patients has been shown to be effective. Incorporating new markers of significant disease as they become available and validated is needed. We need to screen and treat only those most likely to benefit. Finally, as these authors have done, we need to commit to scholarship and the periodic assessment of new information. Such information should lead to refinements in current practice and/or new areas of research. The field of urology will be judged on how it deals with early detection and treatment of PCa. Let's leave a legacy we can be proud of.

Conflicts of interest: The authors have nothing to disclose.

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Reply from Authors re: Allison S. Glass, Matthew R. Cooperberg, Peter R. Carroll. Early Detection of Prostate Cancer: More Information, More Clarity. Eur Urol 2012; 62:753-5

Early Detection of Prostate Cancer: Hope for the Future

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The authors are grateful for the editorial comments of Glass et al. [1]. We are happy that the experts can identify themselves to a large degree with the approach chosen for analyzing the effect of screening on metastatic prostate cancer (PCa) and with the resulting data [2]. A few issues deserve discussion.

We agree that cumulative population-based data on mortality decline and on the decline of metastatic disease through screening cannot be translated easily to individual benefits. The hope is that, in the future, the downsides of screening—specifically overdiagnosis—can be decreased by the use of better diagnostic tests or appropriate risk-stratification tools and by applying screening to large segments of the general population. Then we can anticipate, based on presently available data, (1) that the individual risk of being diagnosed with metastatic PCA or of dying from PCa can be reduced by at least 42% and 29%, respectively, and (2) that this will be important for well-informed men who decide to be tested.

We can identify with the summary of some of our findings [2] given in the subsequent paragraphs of the comment [1]. The authors discuss the issue of a similar rate of M+ disease over time during follow-up. The finding that requires better

understanding in the future is the increase of M+ disease in the screening arm during years 6 and 12. Our interpretation is that this increase is most likely related to the natural treated history of cancers that were present in a fairly advanced stage at the first screen. If this view is correct, we may expect that the rates of M+ disease during follow-up will decrease further in the screening arm once the treated natural history of these cancers has reached its end point.

Glass et al. also address the issue of possible differences in treatment [1]. It is indeed unfortunate that data on treatment by risk group and arm during follow-up are at this time considered to be too incomplete for reporting and statistical analysis. The only available overview report of treatment in the European Randomized Study of Screening for Prostate Cancer (ERSPC) study [3] suggests an imbalance of aggressive treatment in favor of the control arm. In a randomized screening study, it is general policy to leave treatment decisions to regional health care providers to avoid treatment bias. This is also part of our study protocol [2]. Different times of enrollment of study participants between the screen and control arms are an unlikely bias because the time of randomization is time zero for all included men. The earlier time of diagnosis in the screen arm due to lead time and differences of treatment policies that have occurred over almost 20 yr of conducting the ERSPC may have introduced some unidentified bias.

Finally, we agree with the recommendation to replace prostate-specific antigen (PSA) as a screening tool by riskstratifying procedures that already allow avoidance of unnecessary biopsies and selective diagnosis of aggressive cancers. In addition, we agree with the suggestion that, for the time being—short of introducing population-based use of PSA-driven testing-structured, well-designed, and validated counseling of men who wish to be tested for PCA should be standard procedure. Contrary to the US Preventive Services Task Force recommendations, in our view, and considering the present knowledge of risks and benefits, health professionals should be allowed and encouraged to offer this option to men at risk. The authors are happy that the Société International d'Urologie has commissioned the production of balanced information for men at risk and for their health care providers.

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