

PSA Screening Decision-Making Aid

For Patients, General Practitioners and Urologists

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PSA Testing for Patients: Test or Not To Test?

Prostate health is a serious concern for men as they get older. PSA is a blood test to check the health of your prostate, a gland that helps reproduction.

A PSA test shows the levels of prostate-specific antigen (PSA) in your blood. High levels of PSA may suggest a possible abnormal growth of the prostate that may be or may not be cancer.

No test is perfect. There are advantages and disadvantages to PSA testing. Discuss your situation with your doctor to decide if PSA testing is right for you.

The following information may help you decide what questions you want to ask your family doctor or urologist. Together you will choose the best course of action for you.

Advantages

Disadvantages

If you get a normal result with no sign of cancer

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| <ul style="list-style-type: none"> • The result may put your mind at ease | <ul style="list-style-type: none"> • No test is perfect. Sometimes results are incorrect. The test may suggest a normal prostate when in fact there is abnormal growth (false negative). This can give you a false sense of reassurance, but you may in fact have a condition that requires treatment. |
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If you get a result that shows a possible abnormal growth

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| <ul style="list-style-type: none"> • The test may show early signs of disease before your health is affected". | <ul style="list-style-type: none"> • A test may detect a slow-growing |
| <ul style="list-style-type: none"> • Early treatment can delay the spread of the disease, and improve your chances of cure and a longer life". | <ul style="list-style-type: none"> • This could lead to unnecessary treatment and side effects. |
| <ul style="list-style-type: none"> • If you did not take a PSA test, you may not find the cancer until it is too late". | <ul style="list-style-type: none"> • Testing may give a false positive result, which suggests an abnormal growth when there actually is none". This could lead to: <ul style="list-style-type: none"> • unnecessary further testing • medical complications and side effects • high levels of stress and anxiety |

SIU Decision Aid on PSA Testing

Explanatory Comments for General Practitioners

The Société Internationale d'Urologie (SIU) wishes to provide a balanced and easy to understand decision aid for men who are considering to undergoing testing for prostate cancer (PCA).

In order to support health professionals in this situation, the SIU provides this second document which gives step-by-step information in accordance with the statements made in the document dedicated to men at risk in general to facilitate interaction with their doctors.

The European Randomized Study of Screening for Prostate cancer (ERSPC) shows with an average 11 to 14 year follow up a mortality reduction of 29 – 54% for screened men compared to the control group population. At the same time, a high rate of over diagnosis is confirmed, which, in line with most current guidelines lead the authors not to recommend screening applied to the general population at this time. Taking account of this new information, the guidelines of most leading organizations involved in urological cancer care have been modified to include a statement such that “the decision to screen is one that a man should make with his doctor following a careful discussion of the benefits and risks of screening” (AUA guideline on prostate cancer screening, 2014).

Arguments in favor of screening from the decision aid

1. The PSA test can help find prostate cancer at an early stage, before it leads to complaints.

Data from many studies including the ERSPC show a significant downstaging and downgrading of screen detected prostate cancers. The rate of 2.3% of locally advanced or metastatic disease in screen detected cases is about ten times lower than similar data reported in cancer registries prior to the PSA era. These differences are much larger for cancers found in men who had already been screened with a negative test result. Thus, there is little to say against this correct statement, but it has to be brought into context.

2. If the results of my PSA test are good, I will not worry as much.

This statement is justified, but with important limitations which are difficult to pass on in simple terms without causing anxiety. It is well known from a large prevention trial that many prostate cancers, and even aggressive ones, can be found by routine biopsies in men who have PSA values which are lower than those currently used to indicate a biopsy.

Other available studies fortunately show that most cancers found with very low PSA values (about 75%) are non-aggressive or may even be considered “insignificant” according to standard criteria. ERSPC data confirm that almost all can be found at subsequent testing 2–4 years later. The offer of repeated

testing to men with PSA values below current biopsy indications, together with information mentioned above, is likely to be sufficiently reassuring for most men.

3. If my PSA test comes back with poor results, and I undergo successful treatment, I may have a better chance of a cure and live longer.

The potential advantage in terms of mortality reduction is referred to in the introduction to this decision aid. - Active treatment but also active surveillance of screen-detected cases indeed leads to a very high rate of long-term recurrence-free survival and also to an effective decrease in prostate cancer mortality with respect to those men who do not undergo testing. In considering treatment outcomes, age is obviously an important factor. In previously unscreened men, the effect of screening on average only becomes visible after 9 years of follow-up but this is likely to depend on the prognostic characteristics at diagnosis and on the shorter lead time of aggressive cancers. The effect of screening may increase up to 15 years or longer.

Younger men may be more inclined toward screening, and thus have a better chance of benefitting from it. On the other hand, life expectancy in most Western countries is increasing, and many 75 year-old men may have 15 more years to live. Statement number three is correct, but needs to be matched with harms and downsides to be discussed.

4. If the treatment is successful at an early stage, I may be spared the late symptoms of prostate cancer such as the tumor spreading to other parts of my body (metastases).

Indeed, there is increasing evidence of a relative decrease of the prevalence of metastatic disease in the United States and elsewhere during the era of PSA-driven screening. A sub study within the ERSPC study showed a 31% reduction of metastatic disease by screening at the time of diagnosis and during follow-up combined.. This information will be useful in discussions with men who wish to be screened, since the occurrence of metastatic disease is indeed the main cause of suffering that precedes death by 2 to 3 years.

5. I may miss the chance of a cure and of avoiding death from prostate cancer.

This issue has already been addressed under points 1 and 3. Indeed, the results of the European randomized trials which show significant mortality reductions for screened men are the main basis for the discussion of this issue. One RCT confirms that even in predominantly clinically diagnosed PC, radical prostatectomy provides an advantage in overall and cancer-specific survival.

Arguments against screening from the decision aid

1. **If my PSA value is elevated, but further exams do not show prostate cancer, I will have undergone medical testing for nothing, and this will have caused unnecessary anxiety.**

This point is undeniably correct; the question is how heavy it weighs in the individual's situation. Earlier studies found that "physical discomfort during digital rectal examination and during transrectal ultrasound was reported by 181 (37%) of 491 men and by 139 (29%) of 487 men, respectively; discomfort during prostate biopsy was reported by 64 (55%) of 116 men". At the group level only short-lasting minor effects on health status were described.

2. **The PSA test can miss prostate cancer. After a normal result I may feel relieved to think I am healthy while I'm not, or I may still worry about being sick, but I'm not.**

This statement is reciprocal to statement one of the arguments in favor of testing. The answers in the discussions of this point can be derived from answers given there. Advice for repeating the testing should be differentiated according to PSA levels. For a man with a PSA value above 3, repeat testing every 2 years should be recommended. With PSA 1-2.9 ng/ml, one might consider repeating the test after 2-4 years; repeat testing within the PSA range 0-0.9 ng/ml can be delayed to a 4-8 year interval. Considering the inter-test and biological variation of PSA testing, short-term repeat testing is an option to confirm a given PSA value. The speed of rise of PSA over time, PSA velocity, has been shown not to be useful for screening. This does not preclude that the observation of a rapidly rising PSA is likely to indicate the presence of an aggressive prostate cancer.

A brief answer could be: Yes, cancer can be missed, but your low PSA value is indicative of a low risk of finding a cancer. If we continue searching, we may end up finding a cancer which may never lead to symptoms, and which is not life-threatening. Our best evidence shows that we can detect most cancers that may be present in men like you, still at a curable stage, even if we find them during a future examination

3. **An elevated PSA test may detect a slow-growing tumor that could possibly never give me any trouble.**

Over diagnosis strongly depends on age, life expectancy and tumor characteristics. Within the ERSPC study the rate of over diagnosis based on this definition was estimated to amount to about 50%. Overdiagnosis and usually resulting overtreatment is the main reason why screening for prostate cancer is not considered a health care policy at this time.

What then to tell the man to whom you are speaking? Knowing that we advance the time of diagnosis through testing by about 5–15 years depending on aggressiveness of cancers, we need to consider a long period of follow-up.

Fifteen years seems reasonable if we speak to a man whose life expectancy may be expected to match this period. You should mention that “over diagnosed cancers” can be identified after biopsy with acceptable certainty and that such a man then becomes eligible for active surveillance which at least initially avoids the side effects of treatment.

4. I may have to deal with the possible complications of diagnostic testing and of prostate cancer treatment without having a life-threatening cancer.

The short- and long-term side effects of treatment carry heavy weight in this context, specifically if the possibility of over diagnosis in a given situation is to be considered. A recent study from one of the recognized US expert centers revealed rates of full continence and erectile function of <75% versus >85% and <20% versus >45% for different surgeons working at the same institution.

The recommendation is to take into account the patient’s personality as much as possible when making decisions about testing. Men who are at risk should be aware of the risks of anxiety and depression induced by the diagnostic process, and of the possibility of the serious complications of treatment.

The answer to our patient is rather simple and much in line with the comments on the worry of over diagnosis. A man who considers undergoing PSA testing must weigh the potential benefits against the worries. After having gone through all the arguments for and against testing with his GP or urologist, and after having spent some time thinking and discussing the issue with family and/or friends, he should now be able to decide for or against PSA-driven testing.

SIU Decision Aid on PSA Testing

Explanatory Comments for Urologists

The SIU has decided to provide a balanced and easy to understand decision aid to men who are considering to undergoing testing for prostate cancer (PCa). In addition the SIU provides similar documents to support urologists and general practitioners. These documents will be translated into several languages and will summarize in simple wording the potential advantages and disadvantages of undergoing diagnostic testing. In line with most current guidelines, the document concludes that men who consider diagnostic testing for PCA should consult their family doctor and/or urologist and ask for support in this complicated process.

The publication of the 2013 U.S. Preventive Services Task Force

The Recommendation Statement¹ advising against the use of PSA for early detection of PCA has fanned the controversy surrounding the application of PSA-driven testing. In an NEJM "Perspective",² co-authored by Richard J. Ablin, one of the pioneers of the PSA test, the authors conclude that discussions with patients about the benefits and harms of screening are very difficult because of a large number of "layers of uncertainty" which are not resolved by two large randomized studies (the ERSPC and the PLCO study). The present document attempts to unravel these "layers of uncertainty" and to identify what may be considered as "certainties" in the process of interaction between men and their doctors. As a result of the publication of the 11-year update of the ERSPC trial in 2012³ the guidelines of most leading organizations^{4,5} involved in urological cancer care have been modified to include a statement such as "the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences" (AUA guideline on early detection of prostate cancer, 2013.⁴ Screening below age 55 and above age 69 is not recommended or restricted. Clearly, the decision to screen is one that a man should make with his doctor following a careful discussion of the benefits and risks of screening. The present decision aid serves this purpose. The most recent 13-year update of the ERSPC study confirms the previously reported level of relative risk reduction of PCA mortality and shows an increased absolute risk reduction as well as a more favorable "Number needed to invite, NNI" and "Number needed to diagnose, NND".⁶ So far only the Rotterdam center of the ERSPC group has applied an adjustment for non-participation and PSA contamination which shows a significant relative PCA mortality reduction of 51%.⁷

In addition to showing significant reductions in prostate cancer mortality in the ERSPC study as a whole as published in 2009, 2012 and 2014,^{3,6,8} the Swedish and Rotterdam individual center results, published in 2010 and 2013, showed significant PCa mortality reductions^{9,10} (Publication was in line with the 1994 agreements within the ERSPC study group). Still, all conclude that the downsides of screening, mainly the high level of over diagnosis and the side effects due to treatment in general and in potentially "over diagnosed" men, are reasons not to recommend the introduction of population-based screening at this time. This will only change after reliable, complete evaluations of quality of life (QoL) and QoL adjusted life years have shown a generally acceptable balance of harms and benefits which is approached with

the results of the first modelling study of QoL which is based on preliminary ERSPC data¹¹ showing a 23% loss of life years gained after adjustment to estimates of loss of QOL. Nomograms are available to differentiate between “indolent” and aggressive PCA with reasonable certainty on the basis of diagnostic parameters which are part of clinical routine.¹² This will help to avoid unnecessary treatment. The current SIU decision aid aims to facilitate the discussion with men considering prostate cancer testing by providing condensed, state-of-the-art information for our colleagues around the world on the potential benefits and harms of testing for prostate cancer. The present second version of the decision aid is the result of the commitment of the SIU to update this information regularly to adapt to the rapidly changing amount of level one and two evidence.

In the following document, the pro and con arguments of the decision aid designed for men who are considering PSA testing are followed statement by statement in providing background information and explanations to facilitate the interaction between such men and their healthcare advisors. The intention is to keep this document as simple as possible while still taking into account the present situation of continuing controversy.

Arguments in favor of screening from the decision aid

1. The PSA test can help find prostate cancer at an early stage, before it leads to complaints.

- Before the PSA test became widely available in the early 1990s, the diagnosis of prostate cancer depended on rectal examination and complaints that were usually due to the occurrence of metastatic disease. One of the initial reports that led to the use of PSA as a screening test was the one by Catalona¹³ which showed that the proportion of potentially curable cancers could be dramatically increased with the use of PSA as a biopsy indicator. In this context, the differences in the distribution of prognostic factors between the screen and control arm of ERSPC Rotterdam in men aged 55–74 can be considered representative of the “stage shift” that can be achieved with testing. The data show a significant downstaging and downgrading in the screen arm with respect to the control arm (**Table 1**).^{14,15} The rate of T4/N1/M+ disease in screen detected cases is about ten times lower than similar data reported in the Dutch cancer registry prior to the PSA era and three to four times lower than in the ERSPC control group. These differences are much larger for cancers found in men who had already been screened with a negative test result (i.e., men from the second and subsequent rounds of screening in ERSPC).^{16,17} For example, the rate of T3-T4 disease decreased by a factor of 7.1, and similar data were seen for high Gleason scores. Beyond any doubt. This question can be answered positively for previously screened or unscreened men.

2. If the results of my PSA test are good, I will not worry as much

- This statement is justified, but with important limitations that are difficult to pass on in simple terms without causing anxiety. In the control group of the Prostate Cancer Prevention Trial (PCPT) 5519 men who originally presented with PSA values <3.0 ng/ml and were all biopsied during a period of 7 years for PSA ≥ 4.0 or a positive rectal examination (DRE), or at the end of the 7 year study period in 2950 men with PSA values <4.0 ng/ml.^{16,17} A total of 1225 PC were found, a sensitivity (equaling PPV in a setting where all men are biopsied) of 21.9%. The data are unique because they allow us to evaluate the test characteristics of PSA over the whole range of PSA values by including many men who had an end-of-study biopsy without having elevated PSA values. A segment of the data relating to all age groups is included as **Table 2**.¹⁶ These data show that even with PSA values below those currently used for biopsy indication, such as PSA 3.0 ng/ml, many cancers and even about 25% of aggressive cancers as defined by Gleason scores ≥ 7 are found only if all men were biopsied.
- This shows that it is very difficult to reassure a man who is considering testing that a “negative PSA test” gives the certainty to state that there is “no reason to worry”. Some men will consider these figures as sufficient reason to be tested, but some will not. Ways out of this dilemma may be provided by some of the following observations from our literature. Looking at table 2 again, most cancers found with very low PSA values (about 75%) are non-aggressive or may even be considered “insignificant” according to standard criteria. This is also confirmed by observations from ERSPC Rotterdam in 469 men who underwent radical prostatectomy for screen-detected PC. Men with PSA values <3.0 ng/ml at the first screen had cancers classified as “minimal” in 67% of cases.¹⁴ The Malmö Preventive Project Study¹⁸ included 21277 men aged 33-50. Ninety percent of these men had initial PSA values <1.46 ng/ml. With a median follow-up of 23 years, prostate cancer and advanced prostate cancer was clinically diagnosed in 18% and 6.1% of all men. In another report it was shown that repeat screening in men with PSA values <1.0 ng/ml can be delayed for 8 years with only a very small risk of detecting non curable PCA at that time (0.2%).¹⁹ The offer of repeated testing after periods of 2–4 years to men with PSA values below current biopsy indications, together with information mentioned above, is likely to be sufficiently reassuring for most men.

3. If my PSA test comes back with poor results, and I undergo successful treatment, I may have a better chance of a cure and live longer.

- The potential advantage in terms of mortality reduction is referred to in the introduction to the decision aid: screening has been shown in large, well conducted randomized trials to lower prostate cancer mortality in 50–69 year old men by 21–44%, and by 29–56% in those men who were actually tested in the age groups 50–69 years. This information is based on the ERSPC study report of 2012,³ the Göteborg randomized trial of screening for prostate cancer,⁹ the >12year FU data of ERSPC Rotterdam¹⁰ which are both part of ERSPC and the analysis adjusting for contamination and non-participation based on the 2009 ERSPC data.²⁰
- Active treatment but also active surveillance of screen-detected cases is indeed associated with a very high rate of long-term recurrence-free survival and also, as the data of the large European screening studies show, to an effective decrease in prostate cancer mortality with respect to those men who do not undergo testing. A large prospective study in the United States, the CAPSURE project, has recruited more than 10,000 men diagnosed with prostate cancer between 1990 and 2006. Next to the evaluation of trends, follow-up data according to treatment have also become available.^{21,22} The data can be considered population-based, at least for Northern California, and show clearly not only the stage migration that has occurred in the United States, but also the very favorable outcomes of treatment options, specifically for localized disease. Obviously, longer term outcome data are needed, preferably from randomized controlled trials. In considering treatment outcomes, age is obviously an important factor. In previously unscreened men, the effect of screening on average only becomes visible after 9 years of follow-up but this is likely to depend on the prognostic characteristics at diagnosis and on the shorter lead time of aggressive cancers. The effect of screening may increase up to 15 years or longer as shown by the Swedish data, and the question is: how relevant is this in relation to the age of a person who wishes to be screened? Younger men may be more inclined toward screening, and thus have a better chance of benefitting from it. On the other hand, life expectancy in most Western countries is increasing, and many 75 year-old men may have 15 more years to live. The judgment on individual life expectancy is very difficult but necessary. It requires cooperative consideration between a potential patient and his doctor prior to deciding whether to use PSA-driven diagnostic testing. Statement number three is correct, but needs to be matched with harms and downsides to be discussed.

4. If the treatment is successful at an early stage, I may be spared the late symptoms of prostate cancer such as the tumor spreading to other parts of my body (metastases).

- Indeed, there is increasing evidence of a relative decrease of the prevalence of metastatic disease in the United States and elsewhere during the era of PSA-driven screening.²¹ A modeling approach has confirmed these data, specifically for screen-detected cancer, and revealed a high probability that

screening also reduces the absolute risk of suffering from metastatic disease.²³ Within the ERSPC study, a group of four centers had complete 12-year follow-up data available on the occurrence of metastatic disease in the screening and control arms. The study showed a 31% reduction of metastatic disease by screening at the time of diagnosis and during follow-up combined.²⁴

- These data will be useful in discussions with men who wish to be screened, since the occurrence of metastatic disease is indeed the main cause of suffering that precedes death by 2 to 3 years in.²⁴

5. I may miss the chance of a cure and of avoiding death from prostate cancer.

- This issue has already been addressed under points 1 and 3. Indeed, the results of the European randomized trials which show significant mortality reductions for screened men are the main basis for the discussion of this issue. One RCT confirms that in predominantly clinically diagnosed PC, radical prostatectomy provides an advantage in overall and cancer-specific survival.²⁵ The authors of another randomized trial of radical prostatectomy versus observation, the PIVOT study, recently showed that the operation did not have an effect on survival in men with favorable prognostic factors and PSA levels <10 ng/ml at diagnosis.²⁶

Arguments against screening from the decision aid

1. If my PSA value is elevated, but further exams do not show prostate cancer, I will have undergone medical testing for nothing, and this will have caused unnecessary anxiety.

- This point is undeniably correct; the question is how heavy it weighs in the individual's situation. A complete analysis of quality of life effects of screening is now available but addresses QoL effect on a population basis.¹¹
- Early during the ERSPC study, reasons for non-participation and the side effects of the invitation to screening and screening procedures were studied.^{27,28} Main reported motives for refusing to participate were absence of urological complaints (57%) and anticipated pain or discomfort (18%). Significant factors for refusal were older age and a lower level of education. After reading the informed consent form, 49% of men decided to participate in the RCT. Five hundred men were invited to participate in an evaluation of the effects of invitation and of screening on aspects of quality of life. The authors found that physical discomfort during digital rectal examination and during transrectal ultrasound was reported by 181 (37%) of 491 men and by 139 (29%) of 487 men, respectively; discomfort during prostate biopsy was reported by 64 (55%) of 116 men". At the group level only short-lasting minor effects on health status were described. Anxiety was similar in all participants and lasted several weeks in subgroups of men. The findings of low to moderate levels of anxiety of short duration were confirmed in two other independent reports.²⁸⁻³⁰

2. The PSA test can miss prostate cancer. After a normal result I may feel relieved to think I am healthy while I'm not, or I may still worry about being sick, but I'm not.

- This statement is reciprocal to statement one of the arguments in favor of testing. The answers in the discussions can be derived from answers given there. Advice for repeating the testing should be differentiated according to PSA levels. For a man with a PSA value above 3, repeat testing every 2 years could be recommended. If suspicion remains after one or more negative biopsies a multi parametric MRI may be useful. However, its value has not yet been established in properly controlled studies^[31]. With PSA 1-2.9 ng/ml, one might consider repeating the test after 2–4 years; repeat testing within the PSA range 0-0.9 ng/ml can be delayed to a 4–8 year interval. In a recent population based study the effect of PSA levels on mortality reduction by screening was evaluated for men aged 60 years. The data showed that “the ratio of benefits to harms of PSA screening varies noticeably with blood PSA levels at age 60. For men with a PSA level <1 ng/mL at age 60, no further screening is recommended”.³² Considering the inter-test and biological variation of PSA testing, short-term repeat testing is an option to confirm a given PSA value. If data on PSA kinetics are requested, several 3–monthly repeat PSA determinations can be considered. A discussion of PSA velocity, which has been shown not to be predictive in a screening setting,³³ is not considered in the context of this decision aid. PSA risk count, the number of times PSA velocity exceeds a certain PSA velocity threshold, was shown to be predictive in the setting of a one year screening interval.³⁴
- A brief answer could be: Yes, cancer can be missed, but your low PSA value is indicative of a low risk of finding a cancer. If we continue searching, we may end up finding a cancer which may never lead to symptoms, and which is not life-threatening. Our best evidence shows that we can detect most cancers that may be present in men like you, still at a curable stage, even if we find them during a future examination.²⁰

3. An elevated PSA test may detect a slow-growing tumor that could possibly never give me any trouble.

- This statement addresses the important issue of over diagnosis and over treatment. While decreasing prostate cancer mortality in potentially curable aggressive cancers, the stage reduction seen with screening also leads to the detection of cancers that may be considered “over diagnosed”, meaning that they might never lead to clinical detection or life-threatening disease.
- Over diagnosis strongly depends on age, life expectancy and tumor characteristics. Within the ERSPC study the rate of over diagnosis based on this definition was estimated to amount to about 50%,^{35,36} During the first round of screening in ERSPC Rotterdam, 28.9% of the cancers detected were considered to have indolent features and to be suitable for active surveillance.³⁷
- Part of the potential of over diagnosis has been addressed when we discussed the downstaging seen with screening under statement 1 of the

“pro” arguments and in the last paragraph above. Over diagnosis and usually resulting over treatment is the main reason why screening for prostate cancer is not considered a health care policy at this time, just as the investigators of the ERSPC study also concluded.^{3,6,8} However some uncertainty remains. Follow-up times are too short to reliably evaluate inclusion and follow-up criteria as well as trigger points for treatment. In men whose cancers were “re-classified” during follow-up or who chose to be treated by radical prostatectomy, 20–40% must be considered as non-curable based on histological findings and PSA recurrence data.³⁸⁻⁴⁰

- The number needed to screen (NNS) and the number needed to treat (NNT) in the first ERSPC report were 1.410 and 48 after 9 years of follow-up⁸ but changed to 936 and 33 in³ and to 781 and 27 in⁶ after 11 and 13 years. These numbers seem high and are difficult to properly interpret by professionals and lay persons. An attempt of clarification is needed. The figures mentioned are very sensitive to the duration of follow-up, as is evident from the Göteborg study which after 14 years shows an NNS of 294 and an NNT of 12.⁹ NNT also depends on the difference in incidence of PCa between the screen and control arms in randomized trials which is co-determined by the rate of over diagnosis. Future evaluations of the ERSPC study with longer follow-up data will show more conclusively how these figures, which depend on absolute risks and incidence differences between the screening and control arm, will develop over time.
- In the future, if preliminary data are confirmed, multi parametric MRI studies and mpMRI driven biopsy indications may contribute or even provide at least a partial solution of the over diagnosis problem. Using the PIRAD’s (the Prostate Imaging Reporting and Data System) and assigning low scores of suspicion of the presence of PC, several studies claim that about 13–58% of biopsies driven by elevated PSA values and ultrasound guidance can be avoided.⁴¹⁻⁴⁴ In men with normal findings on MRI and in those whose PC was classified as low or intermediate risk with biopsies performed either in bore on the MRI table or by MRI ultrasound fusion about 12–20% of aggressive PC identified by ultrasound guided biopsies were missed.⁴¹⁻⁴³ Follow-up data which would allow to judge on the fate of the missed potentially aggressive cases are not available.
- What then to tell the man to whom you are speaking? Knowing that we advance the time of diagnosis through testing by about 5–15 years depending on aggressiveness of cancers, we need to consider a long period of follow-up. Fifteen years seems reasonable if we speak to a man whose life expectancy may be expected to match this period. To this situation at present the Swedish 14–year data can best be applied (NNS of 294 and an NNT of 12).⁹ It will also be important to mention the outcome of a recent publication on quality of life effects of PSA based screening. Considering the whole expected life span of 1,000 men age 55–69 the model applied reveals a 28% reduction of prostate cancer mortality, 73 life years gained reduced to 56 quality of life adjusted life years (QALY’s) gained, a reduction by 23%. An NNS of 98 and NNT of 5 was reported.¹¹ The model suffers from uncertainties mainly due to assumptions on weighting quality of life effects (utilities).

- How can we deal with this justified worry? If a man is diagnosed with a tumor matching or approaching the definition of “indolent” PC,¹² with PSA <10.0 ng/ml, Gleason score ≤ 6 , T-stage of T1/T2a, PSA density <0.15-0.20, $\leq 50\%$ of PC in any biopsy core, or the inclusion criteria of active surveillance studies such as the PRIAS study,⁴⁵ or the definition of “insignificant”,⁴⁶ could be given the option of “active surveillance”. Short of having a marker that would allow us to diagnose such tumors, active surveillance is the best available option, with so far minimal risks of progression and death from PC.³⁹ However, uncertainties exist at the level of selection and follow-up criteria and can only be clarified with longer follow-up in the ongoing studies. These uncertainties require careful patient information or even formal informed consent. Putting all the information together, we have to answer: “Yes, the uncertainty you are concerned about is legitimate. It should weigh heavily in your decision process”. In the future, if consensus on practice and interpretation can be reached, multi parametric MRI studies or advanced fusion technologies of MRI pictures at TRUS guided biopsies may help to more safely separate aggressive from insignificant cancers.

4. I may have to deal with the possible complications of diagnostic testing and of prostate cancer treatment without having a life-threatening cancer.

- Again, there is little to say against this statement. A given patient has to live with this uncertainty. Figures on negative effects of testing have already been provided in the comments on the first argument against testing; the issue of over diagnosis is addressed in the comments on the third argument against testing.
- The short- and long-term side effects of treatment carry heavy weight in this context, specifically if the possibility of over diagnosis in a given situation is to be considered. In the past, detailed analyses of the worries mentioned in this third argument against screening have been carried out. An older review based on Surveillance, Epidemiology and End Results (SEER data of the years 1989–1991) was presented in.⁴⁷ This analysis has the great advantage of being related to population-based, and not to institutional data which often reflect expert results. The study group reported incontinence (defined as wearing pads) in 7% vs. 22%, and loss of erections in 23% vs. 56% in comparing radiation therapy to radical prostatectomy in men below the age of 70. With the development of less invasive techniques for radical prostatectomy and improvements in radiotherapy, these rates have shown improvement. A recent study from one of the recognized US expert centers revealed rates of full continence and erectile function of <75% versus >85% and <20% versus >45% for different surgeons working at the same institution.⁴⁸ Within the framework of collecting quality of life data related to the different steps of the screening procedure, five-year follow-up data on anxiety and depression and general health-related quality of life of the diagnostic process and of initial treatments were reported in.^{49,50} Surprisingly, the scores for health-related quality of life for treated men with prostate cancer were above those of the normal population. Symptoms of longer term anxiety and depression

persisted in 20-30% of cases. The recommendation is to take into account the patient's personality as much as possible when making decisions about testing. Men who are at risk should be aware of the risks of anxiety and depression induced by the diagnostic process, and of the possibility of the serious complications of treatment.

- The answer to our patient is rather simple and much in line with the comments on the worry of over diagnosis. A man who considers undergoing PSA testing must weigh the potential benefits against the worries. After having gone through all the arguments for and against testing with his GP or urologist, and after having spent some time thinking and discussing the issue with family and/or friends, he should now be able to decide for or against PSA-driven testing. Further risk stratification is possible with the use of risk calculators. Obviously, the man's age, general health state and expectations concerning his personal quality of future life need to be considered.

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Table 1 Patient, pre-treatment and tumour characteristics^{14,15}

	Screening arm n (%) n = 1596	Control arm n (%) n = 464	p-Value
Age (years)	66.5	67.9	p < 0.0001
PSA (ng/ml) mean, median (range)	8.6, 4.9 (0.3-315.7)	57.2, 11.0 (0.3-1500.0)	p < 0.0001
Clinical T stage n (%)			p < 0.0001
T1c	685 (42.9)	117 (25.2)	
T2	530 (33.2)	112 (24.1)	
T3	196 (12.3)	71 (15.3)	
T4/N1/M1	36 (2.3)	47 (10.1)	
Unknown/other (TURP detected)	149 (9.3)	88/29 (19.0)/(6.2)	
Biopsy			
Gleason score* n (%)			
<7	1111 (69.6)	153 (41.0)	p < 0.0001
=7	378 (23.7)	126 (33.8)	
>7	102 (6.4)	93 (5.2)	
Total	1591 (100)	373 (100)	
Unknown	5	45	

* Does not include TURP and cystoprostatectomy in the control arm (n = 54)

Table 2 Sensitivity and specificity for prostate cancer and high-grade disease, by cutpoints of prostate-specific antigen (PSA)¹⁶

PSA ng/mL	Any Cancer (n=1225) vs No Cancer (n=4362)		Gleason Grade ≥7 (n=250) vs Gleason Grade <7 or No Cancer (n=5325)		Gleason Grade ≥8 (n=57) vs Gleason Grade <8 or No Cancer (n=5518)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
1.1	83.4	38.9	92.8	37.0	94.7	35.9
1.6	67.0	58.7	84.4	54.8	89.5	53.5
2.1	52.6	72.5	75.6	67.3	86.0	65.9
2.6	40.5	81.1	67.2	76.5	78.9	75.1
3.1	32.2	86.7	57.6	82.3	68.4	81.0
4.1	20.5	93.8	40.4	90.0	50.9	89.1
6.1	4.6	98.5	13.2	97.8	26.3	97.5
8.1	1.7	99.4	4.8	99.0	10.5	99.0
10.1	0.9	99.7	2.4	99.5	5.3	99.5

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