

Prostate Cancer Screening with Prostate-Specific Antigen Testing: More Answers or More Confusion?

Prostate cancer is a leading cause of morbidity and mortality among middle-aged and older men. Of the solid tumors prostate cancer is rather unique in that it presents in 2 distinct forms, a latent form, which grows slowly and poses no threat to the patient's life, and an aggressive form, which metastasizes quickly and kills the patient. The discovery of prostate-specific antigen (PSA)² and the demonstration of its utility for early diagnosis and monitoring of prostatic carcinoma have raised hopes that this simple serological test could be invaluable in screening asymptomatic individuals for early prostate cancer diagnosis. The premise is that such early diagnosis may then lead to early therapeutic interventions, which should improve the overall survival of prostate cancer patients. However, PSA screening of asymptomatic individuals has remained controversial during the last 15 years owing to the lack of evidence for improved patient survival. Recently, the results of 2 major randomized clinical trials on the effectiveness of PSA as a screening tool, from both the US and Europe, have been published. These results are not clear cut. For this reason, the controversy surrounding prostate cancer screening will likely continue for years. Below, we examine this issue with 4 authorities in the field.



What do you think is driving the widespread use of PSA testing for prostate cancer screening over the last decade, despite the absence of evidence for its benefit?

Patrick Walsh³: Undisputed evidence for benefit! There is no debate that PSA testing has made it possible to diagnose prostate cancer at an earlier, curable stage. Because prostate cancer produces no symptoms until it is far advanced, before PSA testing most

patients presented with incurable disease—either locally advanced or metastatic. However, following the advent of PSA testing, suddenly it became possible to diagnose prostate cancer at an earlier curable stage. According to data from the American Cancer Society, in 1990 only 68% of men presented with localized disease and 20.6% had metastatic disease. In 2009, 91% of patients presented with localized prostate cancer, only 4% had metastatic disease, and deaths from prostate cancer between 1996 and 2006 fell from 41 400 to 27 350. To answer the question more succinctly, PSA testing has given men a choice that they did not have before it was available: men can either undergo testing and if they have cancer choose treatment or observation or they can do nothing and run the risk of a diagnosis when it's too late to cure.



Klaus Jung⁴: PSA has become the most popular tumor marker ever because of its relationship with tumor stage and because of the increasing risk of developing prostate cancer with increasing PSA, as demonstrated on the basis of PSA results obtained many years before diagnosis. None of the biomarkers for other cancers has been shown to be comparably

effective in detecting a carcinoma at a stage early enough for curable treatment that would reduce the prevalence of primary metastatic carcinoma. Despite all problems resulting from noncancer-related biological factors affecting PSA concentrations (e.g., intra- and interindividual biological variability of PSA, age, prostate volume, possible inflammation) as well as analytical issues like insufficient interchangeability of PSA obtained by

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² Nonstandard abbreviations: PSA, prostate-specific antigen; ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal

and Ovarian Cancer Screening Trial; PCA3, prostate cancer 3; MRT, magnetic resonance tomography.

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different commercial PSA assays, there is currently no alternative to PSA and for the urologist this marker will remain the early biochemical signal of prostate cancer in the near future.



William Catalona⁵: The short answer is, “Because it works.” Patients and physicians have relied upon the test because it gives them valuable information that they want to have, and death rates have continued to fall during the PSA era.

Clinicians have learned from their own experience that, although the PSA test is not perfect, it is effective in identifying men at high risk for prostate cancer and for detecting it early. Approximately 10% of men over 50 have a PSA >4 $\mu\text{g/L}$, and approximately 20% have a PSA >2.5 $\mu\text{g/L}$. These men are at far greater risk for prostate cancer than the approximately 80% with lower PSA levels. Moreover, there is also a strong correlation between PSA and the aggressive form of the disease.



Neil Fleshner⁶: PSA screening continues despite conflicting evidence for its survival benefit. There are a variety of factors driving this. First, it is important to recall the landscape with respect to prostate cancer detection before the PSA era. In the late seventies and early eighties, a high proportion

of patients with prostate cancer detected by digital rectal examination alone had a high probability of node-positive disease in addition to having a greater chance of extraprostatic extension.

The second reason for ubiquitous PSA screening relates to the favorable early and midterm outcomes reported among patients who have had PSA-screened tumors. The rate of organ-confined disease as well as improved functional outcomes due to the

nature of nerve-sparing surgery, particularly among patients with early stage disease, has improved outcome.

Question # 2: Mortality from prostate cancer in the US has fallen by about 4% per year since 1992. Is it because of the voluntary PSA screening or some other reasons?

Patrick Walsh: The introduction of any new form of treatment for localized prostate cancer requires at least 10 years before a major effect on mortality is seen. The dramatic decline in mortality since 1992 is the result of 2 events—earlier diagnosis at a curable stage and effective therapy. In 1982, only 7% of men with localized prostate cancer underwent surgery and radiation therapy was too underpowered to cure. Almost no one received treatment with curative intent. However, a decade later, when more men with curable disease were identified and the side effects of radical prostatectomy were reduced, more than 100 000 men underwent surgery. If one applies the findings of the Scandinavian Prostate Cancer Group’s randomized trial of surgery vs watchful waiting to these men, 7500 to 15 000 fewer men per year should be dying of the disease or suffering from painful metastasis. This, coupled with improvements in radiotherapy, are the reasons why fewer men are dying of the disease.

Klaus Jung: This is too complex a question to be answered with a single reason. Following the introduction of PSA screening at the end of the eighties, there has been a continuous decline of the prostate cancer death rate in ensuing years. The influence of PSA screening on the decreased mortality rate seems to be more than likely, but it has not been proven. There are arguments that the decrease of prostate cancer mortality was observed too early after the introduction of PSA screening for prostate cancer, a slow-growing carcinoma with a long biological history. Thus, the mortality decline is probably a combined result of the more frequent detection of prostate cancer at an early, curable stage by PSA screening and the improved treatment modalities such as surgery, radiation, and hormonal therapies during the later years. For example, for patients who have a higher risk of recurrence, there is an improved postoperative strategy with early adjuvant radiation and prolonged hormonal therapy. Radiation therapy now uses a higher dose (approximately 80 Gy) to cure prostate cancer in comparison to earlier years.

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In addition, successful options for advanced stage patients with asymptomatic metastases (zoledronic acid, chemotherapy with docetaxel) improve survival. However, it also should be mentioned that death misclassification bias and the use of statins have been discussed as contributing to the decline of the prostate cancer mortality rate.

William Catalona: It is mainly because of PSA screening. Of course, other factors come into play, such as improved treatments and their earlier application. Nevertheless, it has been estimated that 40% to 75% of the reduction is due to PSA screening.

One cannot completely dissociate the effects of screening from treatment. Early detection would be useless without effective treatment. And curative treatments are effective mainly in patients with early disease. However, the most effective curative treatment, radical prostatectomy, was available before the PSA era. Therefore, PSA screening is the most important factor responsible for the falling mortality rate.

Neil Fleshner: It is of course impossible to know for sure the impact of PSA screening on mortality rates. However, if one looks at the early European Randomized Study of Screening for Prostate Cancer (ERSPC) trial results there appears to be a benefit in mortality in prostate cancer noted as early as 8–10 years after instituting a screening period.

Furthermore, we know from the Swedish randomized trial of prostatectomy vs watchful waiting, that mortality rates start to split similarly at approximately 7–9 years. I think it is therefore quite plausible that screening or early detection has been in part responsible for the falling US mortality rates. I also believe that PSA as a marker in detecting early recurrence, and in particular with the use of early hormone therapy that arises from PSA testing, may have also improved prostate cancer mortality.

Question # 3: Why do you think that the 2 large, randomized trials on prostate cancer screening reached seemingly contradictory results? (New Engl J Med 2009;360:1310–9 and 1320–8.)

Patrick Walsh: This question is easy to answer. One of the trials, the ERSPC, was well done and informative. The other trial, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), was poorly done and uninformative. The ERSPC was a landmark study carried out in 7 countries that enrolled 162 000 men with follow-up out to 14 years. In patients who were actually screened, there was a 27% decrease in prostate cancer deaths. The PLCO, which was half the size of the European Trial and had complete follow-up half as long (7

years), concluded that screening had no effect on prostate cancer mortality. This study contained numerous flaws. (a) The follow-up was too short. Screening and aggressive treatment are typically reserved for individuals with at least a 10-year life expectancy and any patient who dies within 7 years of diagnosis had incurable disease at the time of diagnosis and would have not benefited from screening. In the positive ERSPC trial there was also no improvement in survival before 10 years. (b) The trial did not test screening vs no screening but rather more screening vs less—85% of patients in the screened arm underwent PSA testing compared to 52% in the controls. (c) Forty-four percent of the men who entered the trial already had 1 or more PSA tests. Consequently, these men were not only less likely to have cancer, but also less likely to have life-threatening disease. This is why so few men died from cancer and why there was no decrease in advanced disease in the men who underwent screening. (d) Only 30% of the screened men who developed a PSA >4 ng/mL while in the trial actually underwent a biopsy. Indeed, if the authors had set out to design a study to discredit PSA testing it would have been difficult to do a better job.

Klaus Jung: The different study designs are clearly responsible for the contradictory results (e.g., the PLCO trial with 73 000 men between 55–74 years used annual screening with a PSA decision threshold of 4 $\mu\text{g/L}$; the ERSPC trial with 162 000 men between 55–69 years applied a PSA cutpoint of 3 $\mu\text{g/L}$ and mean screening interval of 4 years, but using different recruitment and randomization procedures between the participating countries). Both studies had limitations. The PLCO trial manifested distinct weaknesses of the study design, (a) with PSA prescreening activities in about 40% of the study participants before randomization, leading to the probable elimination of men with prostate cancer from the study groups; (b) the relatively small numbers of participants; (c) the high PSA contamination rate in the control arm, leading to a comparison of 2 different “screening” cohorts with 85% and 52% PSA tests performed; and (d) the limited duration of follow-up of 7 years. Thus, it was not really surprising that a decrease of prostate cancer mortality as the benefit of screening could not be seen. Even if the patient number in the ERSPC study is higher but still relatively small, the first results show a benefit; with adjustment for nonattendance in the screening arm (defined as failure to attend the initial screening round) and PSA contamination in the control arm (defined as carrying out at least 1 PSA test after randomization) the reduction in mortality is already 31%. If these results would have been published before the PLCO data, the nega-

tive discussion concerning the effectiveness of PSA screening probably would have not taken place.

William Catalona: The European trial (ERSPC) provides conclusive evidence that PSA screening can save lives; whereas, the US trial (PLCO) is essentially non-informative on this issue. Moreover, it is likely that the mortality benefit in ERSPC is an underestimate because of the relatively short follow-up, the relatively long screening interval, the nonuse of digital rectal exam as a screening test after the first round, and contamination in the control arm. In contrast, it is unlikely that PLCO results will change substantially with further follow-up because the study was fatally flawed from the beginning. The most serious flaws are:

1. More than 43% of participants were prescreened, eliminating many men with high-risk prostate cancer from the study population (prescreened men had a 25% lower prostate cancer mortality rate) and reducing the power to detect a mortality difference.

2. More than 52% of controls were screened during the study. This contamination reduces the differences in prostate cancer mortality rates and also exaggerates the estimates of the number-needed-to-treat to save 1 life.

3. PLCO had no requirement for men with abnormal screening results to undergo biopsy, and only approximately 40% of men with abnormal screening results underwent biopsy within 1 year, thus compromising early detection and prompt treatment.

4. It takes patients a median of 13 years after biochemical recurrence following radical prostatectomy to die of prostate cancer. However, the median follow-up for men with cancer in PLCO of 5–6 years was insufficient to evaluate mortality results.

5. PLCO included men up to age 74 years who are less likely to have a mortality benefit from screening.

In summary, ERSPC provides level 1 evidence that PSA screening reduces prostate cancer mortality by at least 20% (as stated above, by 31% after correction for noncompliance with screening in the screening arm and contamination in the control arm), with the authors expressing concern about detecting tumors that might never threaten the participant's life.

In contrast, PLCO is noninformative about the potential benefits of screening using current PSA parameters (2.5 $\mu\text{g/L}$ cutoff, PSA velocity, PSA density, % free PSA) for biopsy (with a 12-core biopsy) for healthy young men who respond promptly to abnormal findings and undergo prompt, effective, high-quality treatment.

Neil Fleshner: The 2 recent large randomized trials of prostate cancer screening published in the *New En-*

gland Journal of Medicine offer a very interesting dilemma. Although not published in the *New England Journal* manuscript, data from a prior PLCO publication have shown that upwards of 40% of patients with an abnormal PSA in the study never got a subsequent biopsy. Add to this the large number of patients who received a PSA test in the control group. In my view this has led to a severely contaminated study within the PLCO cohort. That is the reason, in my opinion, that this led to a null result. Therefore, the European study is more representative of the true effect of PSA screening at an 8–10 years time point.

Question # 4: Do you think the data released by the 2 aforementioned studies were premature? And should we expect more updates? And when? Could these updates substantially change the picture we have now?

Patrick Walsh: By design, the ERSPC was required to release data when the critical threshold for efficacy was demonstrated. Much has been made of the fact that to prevent 1 prostate cancer death at 10 years, 1400 men would need to be screened and an additional 48 men would need to be treated. However, because screening resulted in a 41% decrease in the number of men with incurable disease, with longer follow-up the number needed to treat will fall. In contrast, the PLCO trial never reached the critical threshold necessary for reporting results and there is much speculation that the trial was published at this time to dampen the enthusiasm generated by the European trial. Because screening in this study did not improve clinical stage, with longer follow-up the results will not change.

Klaus Jung: With the behavior of prostate cancer and its mostly slow progression as well as with the lead-time of 5–12 years defined as the period from PSA screening detection until clinical diagnosis of cancer, it can be anticipated that the PLCO study with a median follow-up of 7 years and the ERSPC study with a median follow-up of 9 years presented data prematurely. Further results can only strengthen the effectiveness of PSA screening. Follow-up in the PLCO study is scheduled for at least 13 years for all participants. However, whether the PLCO trial will ever show a difference with the 2 cohorts is highly questionable because of the persisting effects of prescreening before randomization and of PSA contamination in the control arm. Also the ERSPC study will continue to follow patients and will analyze in addition to the primary endpoint of mortality, like the PLCO trial, the effect of PSA screening on important aspects of quality of life and cost-effectiveness. Further results of the ERSPC have more potential to show an increasing PSA benefit. Because

patients who present with metastatic disease can survive 10–15 years and longer, it is difficult to foresee an optimal timeframe. But updates every 4 years after each round of rescreening should be favored.

William Catalona: In my opinion, the PLCO data were released prematurely. One must question why this flawed study was rushed to simultaneous publication in the same journal as the milestone European study that provided the first conclusive evidence that PSA screening saves lives. The biased media coverage of PLCO diminished the impact of the validation of PSA screening by ERSPC and created confusion among patients and physicians who did not appreciate the relative strengths and weakness of the 2 trials.

No doubt, there will be updates from both studies. ERSPC will show a greater mortality benefit and correspondingly lower numbers needed to screen and to treat to save 1 life. Although it is possible that updated PLCO might show a mortality benefit for screening, because of the fatal flaws in PLCO's study design, they will not accurately reflect the true benefits of screening.

Neil Fleshner: As one contemplates the natural history of screen-detected prostate cancer where significant lead-time biases exist, I believe that the results were prematurely released. Prostate cancer is a slow growing disease unlikely to pose an important risk to patient mortality for between 10 and 20 years after detection. With this in mind, I believe that a further update of these studies will provide a clearer answer about the role of screening. I do not know exactly when these updates will come. I do believe that longer-term data will, however, demonstrate a superior mortality benefit particularly in the European study where there has been minimal contamination of the control group with PSA exposure. I do believe the other competing force is overall mortality from increasing patient age and it is of course impossible to predict how that will impact the survival curves. Nevertheless, it is certainly my view that the benefits of screening will become apparent and likely more substantial with time.

Question # 5: *Based on the released data, would you recommend PSA screening to your patients? How would you justify your recommendation (yes or no) to them?*

Patrick Walsh: My recommendation is simple. I tell patients that if they are the kind of person who doesn't wear a seatbelt nor goes regularly to the dentist or their family doctor for a check up and doesn't worry about dying from prostate cancer, they should not undergo PSA testing. On the other hand, if they are a healthy

man age 55–69 who does not want to die from prostate cancer, the European trial provides conclusive evidence that PSA testing can save their life.

Klaus Jung: The data support the approach practiced in our clinic to recommend PSA testing but only to informed patients. Thus, the urologist, before ordering the blood test, should be obliged to inform patients about the limits, advantages, and disadvantages of PSA screening and its possible consequences with regard to possible treatment side effects and treatment options, including active surveillance. This decision is justified with the 31% reduction of mortality in the European study. Our experience has shown that even patients with "insignificant" tumors as candidates for active surveillance decide in favor of surgical or radiological treatment due to the permanent anxiety of disease progression. The indisputable correlation of PSA with prostate cancer and the 80% reduction of patients presenting with metastatic disease after introducing PSA are further arguments to recommend PSA screening.

William Catalona: Yes, I recommend PSA screening to my patients. I justify this because it would provide them with the best estimate of their risk for having prostate cancer and the greatest chance of avoiding death from this disease.

Neil Fleshner: Because the number needed to treat among patients at higher risk of disease is smaller, I would be more proactive with patients who are at higher risk of prostate cancer such as men with positive family histories or men of African descent. It is also possible that in the future, a variety of men with certain genotypes may be also better suited for screening.

I would emphasize to men before screening that certainly not all men diagnosed with prostate cancer require active therapy. Active surveillance is now a viable option for the majority of men and I would explain this to patients a priori. I believe that the incorporation of active surveillance into screening protocols may be a viable way to minimize overtreatment and maximize serious case detection and thus maximize overall outcomes.

Question # 6: *Did you ever measure your own PSA and why or why not?*

Patrick Walsh: When I was young I watched 3 of my uncles die from prostate cancer. I wonder how many critics of PSA testing have actually seen a man with metastases die of the disease? Do they understand that from 1995 to 2004 PSA screening and effective treatment have reduced the age-adjusted rate of prostate cancer death in the US by 37%? I have a PSA <3 ng/mL

and have had yearly PSA measurements since 1991 and will do so until I am 75 years of age.

Klaus Jung: Yes, I did this several times in the last years in contrast to the general urologic guidelines. The reason is that we do PSA research and because there are few men in our laboratory. I have regularly provided blood for experiments. The technicians appreciate the offer with a complete PSA profile with different assays!

William Catalona: Yes, to determine my risk for prostate cancer.

Neil Fleshner: Yes. I have a strong family history of prostate cancer. I measured my first PSA at age 40 and have continued with yearly measurements since.

Question # 7: Can you identify a possible scenario (e.g., with a better marker or imaging) by which the side effects of screening (overdiagnosis and overtreatment) would be eliminated or diminished?

Patrick Walsh: Yes, better imaging. At the present time we are not able to identify the exact location and extent of cancer within the prostate. One day when this is possible, we will be able to identify those patients who are diagnosed with tumors that are too small to treat and monitor them more accurately for progression.

Klaus Jung: I would distinguish 2 possible scenarios, the current and the future one. Taking into account the current knowledge of all cancer-related factors and their relationships, I suggest a multifactorial approach of risk calculation to avoid overdiagnosis. Since 2003 we have used an artificial neural network in our clinic to avoid unnecessary biopsies. This software calculates the possible risk of prostate cancer on the basis of age, prostate volume, and results of the digital rectal examination, together with total and percent free PSA. Other risk calculators are freely accessible on the internet. We see more and more well-informed patients, who want to use all options before biopsy, including this artificial neural network and new markers like prostate cancer 3 (PCA3). The current screening situation may improve with some new blood and urine markers with initial, promising results. So far, only those markers which can be used on a commercial basis, like PCA3, or soon –2proPSA, have a theoretical chance to improve screening (especially for aggressive cancer) as adjunct markers in addition to PSA and percent free PSA. Other markers including the gene fusions still have a too low sensitivity and are not commercially available so far. Also, considering PSA velocity on an individual basis without strict cutoffs often does help to make the right biopsy decision. Further, with contrast-enhanced

prostate biopsy strategies or magnetic resonance tomography (MRT)-based prostate biopsies we could increase the cancer detection rate. Thus, overdiagnosis can be currently diminished with careful selection of patients for biopsy, while overtreatment can be reduced by careful counseling of patients with newly diagnosed prostate cancer.

The future scenario will be determined by the main unresolved problem of detecting only aggressive types of prostate cancer by use of noninvasive biomarkers. The challenge is to identify those tumors that would progress and metastasize if left without treatment. The intensive search for better markers based on new “-omics” approaches, and, the development of reliable mathematical models that combine all relevant clinical and biochemical data are the essential aims. The future of prostate cancer screening would be most likely a combination of serum and urine markers and multivariate models. The task of the clinical chemist will be the translation of basic research in genomics, transcriptomics, proteomics, and metabolomics to develop reliable noninvasive markers in blood and urine as diagnostic and prognostic indicators. In strong cooperation with clinicians, laboratory scientists can contribute importantly with their experiences in analytical and preanalytical issues as well as in data interpretation.

William Catalona: Unfortunately, to date, there has not been a validated test that is superior to PSA as a screening device. There is always hope that the PSA test, itself, may be further refined, or that some other test would be discovered that would be even more precise.

The intelligent use of such tests could certainly diminish, but never completely eliminate, overdiagnosis and overtreatment.

Neil Fleshner: I believe novel biomarkers may play a role in diminishing the overtreatment situation that exists with respect to PSA screening. However, this remains speculative and further data are needed.

As alluded to earlier, active surveillance in combination with screening would be a reasonable way of minimizing overtreatment of patients who would otherwise not require therapy for prostate cancer. Active surveillance is becoming an increasingly common option for these men. This involves serial determinations of PSA and periodic prostate rebiopsies with intervention only when certain disease parameters become more evident such as an increase in histologic grade or volume of cancer. The safety of active surveillance has been well demonstrated in the 7–10-year range in a variety of cohorts. A randomized trial is currently underway. My personal impression is that logically speak-

ing, active surveillance would be a safe option for the majority of men diagnosed with low-volume, low-grade disease.

Another strategy that may be emerging as an alternative to the side effects of radical therapy is focal therapy. This involves using modalities such as high-intensity focused ultrasound, heat, or cooling to destroy prostate tissue. With minimally invasive techniques combined with magnetic resonance or ultrasound guidance, the idea behind this novel paradigm is to eliminate the sector of the prostate containing prostate cancer without eliminating the whole gland. The rationale is to produce minimal sexual and urinary side effects while achieving local cancer control. The long-term efficacy of these modalities remains to be determined. Of course the natural multifocal nature of prostate cancer poses some concern about this approach. However, multiple small foci of prostate cancer may have little effect in a patient during their lifetime.

Question # 8: Do you have any other general or specific comments on this topic?

William Catalona: In the final analysis, prostate cancer is the second leading cause of cancer death in men in the US as well as many other countries. It arises silently and remains in a curable stage for a time before passing silently into an incurable stage. There is no established method for preventing aggressive prostate cancer and no means of curing it once it has reached an advanced stage. Thus, to reduce suffering and death from prostate cancer, it must be detected early, and the most effective method of early detection is PSA screening.

Once the diagnosis of cancer is established, the need for treatment must be assessed by evaluating the features of the tumor and of the patient.

The ERSPC has established that cure is possible when necessary by showing a 20% reduction in prostate cancer mortality among screened men (and, as stated above, 31% reduction after adjusting for non-compliance and contamination). Validating this mortality benefit are data showing a 40% decrease in the US prostate cancer mortality rate and data from the World Health Organization, revealing a similar mortality pattern in countries where PSA screening is practiced, and stable or increasing rates where it is not.

The goal of screening is to detect cancers that

could cause suffering and death, but screening may also detect cancers that would never cause symptoms. Currently, because of limited ability to distinguish between harmless and lethal cancers, most cancers are treated.

Active surveillance and focal therapy have emerged as strategies to guard against overtreatment; however, physicians should be careful not to throw out the baby with the bath water. With surveillance or focal therapy, potentially life-saving treatment may be delayed in patients with an initially undergraded or understaged tumor. Some will slip through the cracks and will be forced to endure unnecessary suffering and death from prostate cancer.

“Underdiagnosis” and “undertreatment,” i.e., the detection of cancers that have spread beyond the prostate and unnecessary delay in adequately treating curable ones, respectively, are also important concerns that have received much less attention than overdiagnosis.

Finally, the onus is on treating physicians to ensure that patients receive effective, high-quality treatment to maximize cure rates and minimize side effects.

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