Prostatic Specific Antigen for Prostate Cancer Detection

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ABSTRACT

Prostate-specific antigen (PSA) has been used for prostate cancer detection since 1994. PSA testing has revolutionized our ability to diagnose, treat, and follow-up patients. In the last two decades, PSA screening has led to a substantial increase in the incidence of prostate cancer (PC). This increased detection caused the incidence of advanced-stage disease to decrease at a dramatic rate, and most newly diagnosed PC today are localized tumors with a high probability of cure. PSA screening is associated with a 75% reduction in the proportion of men who now present with metastatic disease and a 32.5% reduction in the age-adjusted prostate cancer mortality rate through 2003. Although PSA is not a perfect marker, PSA testing has limited specificity for prostate cancer detection, and its appropriate clinical application remains a topic of debate. Due to its widespread use and increased over-detection, the result has been the occurrence of over-treatment of indolent cancers. Accordingly, several variations as regards PSA measurement have emerged as useful adjuncts for prostate cancer screening. These procedures take into consideration additional factors, such as the proportion of different PSA isoforms (free PSA, complexed PSA, pro-PSA and B PSA), the prostate volume (PSA density), and the rate of change in PSA levels over time (PSA velocity or PSA doubling time). The history and evidence underlying each of these parameters are reviewed in the following article.

Key words: prostate cancer; diagnosis; prostate-specific antigen; biopsy
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INTRODUCTION

Prostate-specific antigen (PSA) was approved by the United States Food and Drug Administration (FDA) in 1986 to monitor men with prostate cancer (PC). In 1994, it was approved for cancer detection. PSA testing revolutionized our ability to diagnose, treat, and follow-up patients. In the last decades, PSA screening has led to a substantial increase in the incidence of PC. This increased detection has caused the incidence of advanced-stage disease to decrease at a dramatic rate, and most recently diagnosed PC today are localized tumors with a high probability of cure (1).

Despite the shift toward improved detection and early diagnosis, controversy still exists regarding the merits of screening. As a result of PSA screening, the lifetime risk of being diagnosed with PC has increased to 16%, whereas the risk of dying from the disease is only 3.4% (2). Increased detection of slow-growing or relatively benign cancer can be a contributing factor to the large discrepancy between incidence and mortality rates. These cancers do not necessarily require definitive treatment, raising concerns about overdiagnosis and overtreatment. Patients with non-life-threatening disease may unnecessarily be exposed to sexual, urinary, and bowel dysfunction that can occur after any therapy for PC (3).

There is currently no consensus among health organizations regarding routine PSA screening for PC. Opponents claim there is no conclusive evidence that

early detection and treatment influence the overall death rate, and screening can result in great morbidity. However, there is evidence that screening is responsible for a decrease in cancer-specific mortality. Bartsch et al. assessed PC mortality in Tyrol, Austria. In this region, 86.6% of men had gone through PSA testing at least once, and radical prostatectomy was the primary treatment option. Cancer mortality declined at a significantly faster rate in Tyrol than in the rest of Austria, where screening was not as widely used (54% vs. 19%, P = 0.001). The investigators concluded that the reduction in mortality was probably due to early detection, consequent down-staging and effective treatment (4).

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer are two large, randomized studies addressing the question: does screening improve prostate cancer-specific mortality? It is hoped that both studies can provide further insight into PSA testing and its role in reducing prostate cancer mortality.

PSA is a valuable tool for detecting PC, but it is not perfect. The test lacks both the sensitivity and specificity to accurately detect the presence of PC. PSA is a prostate-specific marker, not a PC marker. Elevated levels in the blood may be driven by conditions such as benign prostatic hyperplasia (BPH) and prostatitis (5). None of the PSA cut-offs currently in use consistently identify patients with PC and exclude patients without cancer. PC incidence in patients with PSA levels below the accepted level of 4.0 ng/mL is similar to the incidence of prostate cancer in patients with PSA between 4.0-10.0 ng/mL, which leads some experts to state that it should not be used as a PC marker (6).

The issues regarding PSA accuracy have led investigators to evaluate additional methods of analyzing PSA data, including the use of PSA derivatives and others biomarkers to improve PSA efficacy in detecting PC. Despite the discovery of many new biomarkers, only a few have shown some clinical value.

PSA BIOLOGY

PSA is a serine protease member of the human kallikrein family. It is produced in both normal and cancerous prostate tissue and secreted into seminal fluid. Its physiologic function is to liquefy semen from its gel form (7). Normal prostate architecture keeps PSA confined to the gland, and only a small portion is leaked into the circulation. PSA circulates in free and complexed forms. Free forms represent 5%-35% of total PSA. Complexed forms (65%-95%) are bound to protease inhibitors. Binding inactive protease and PSA in the blood has no catalytic activity (8).

Serum PSA elevations occur as a result of disruptions in the prostate architecture that allow PSA to enter the circulation. This can occur in disease settings (PC, BPH, or prostatitis) or after prostate manipulation (massage, biopsy, or transurethral resection). Increased levels in PC patients cannot be explained by increased synthesis. In fact, PSA expression is slightly decreased in cancer tissue (9).

PSA expression is strongly influenced by androgens. Patients using 5α-reductase agents such finasteride and dutasteride show a 50% decrease in detectable PSA level and should have their level doubled to reflect the correct estimated PSA level (10).

Ethnicity, age, and body mass index (BMI) can also influence PSA levels. Black men without PC show higher levels compared with white men, probably reflecting a higher expression by benign prostate tissue (11). Lower levels of PSA in obese men, which may be related to the influence of estrogen, can mask the presence of significant cancer (12).

PSA AS A DETECTION TOOL FOR PROSTATE CANCER

Prostate cancer risk varies according to serum PSA levels. Initially, a threshold of 4.0 ng/mL was recommended as the level at which a man should undergo prostate biopsy. This value was based on studies on healthy men showing that 97% of men older than 40 had PSA levels ≤ 4.0 ng/mL. Sensitivity and specificity of this threshold were 20% and 94%, respectively (13). Moreover, the 4.0 ng/mL threshold has a positive predictive value of only 37% and a negative predictive value of 91%, which translates into a 25% probability that a man in the 4.0-10.0 ng/mL zone has cancer (14).

Since prostate biopsies are rarely performed on men with low PSA levels, specificity and sensitivity of PSA are more difficult to validate. The Prostate Cancer Prevention Trial was the first study to assess PC incidence and aggressiveness in men with low PSA levels and a normal digital rectal examination. The trial was designed to examine the association between finasteride and PC risk; prostate biopsies were offered to all men in the placebo arm at the end of the 7-year study. Overall, cancer detection in the placebo group was 15%, and high-grade prostate cancer was found in 15% of the patients. Among men with PSA levels ≤ 0.5, 0.6-1.0, 1.1-2.0, 2.1-3.0, and 3.1-4.0 ng/mL, the incidence of prostate cancer was 7%, 10%, 17%, 24%, and 27%, respectively. The cancer incidence in patients with PSA levels above 2.0 ng/mL differed only slightly from those with PSA between 4.0 and 10.0 ng/mL (15). This study revealed that PC is not rare with a PSA below 4.0 ng/mL, and aggressive PC was found even in patients with PSA levels below 1.0 ng/mL.

Table-1 shows the sensitivity and specificity of different PSA thresholds. Attempts to improve detection by lowering the PSA threshold are subject to a higher false positive rate. For example, lowering the threshold to 2.6 ng/mL would raise sensitivity to 40%, but it would increase the false positive rate to 18.9%, translating into more unnecessary biopsies. Thresholds higher than 4.0 ng/mL would miss some aggressive diseases. Catalona et al. demonstrated that one third of prostate cancers detected with PSA

above 4.0 ng/mL already had extracapsular disease, and the likelihood of having organ-confined disease at radical prostatectomy was 81%, 74%, and 72% in men with PSA levels of 2.6-4.0, 4.1-7.0, and 7.1-10.0, respectively (16).

Positive PC familiar history is also important. In those men, the likelihood of PC diagnosis in is 20%, 13%, 17.9%, 29.4% and 77.8% in men with PSA levels of < 0.5, 0.5-1.0, 1.1-2.0, 2.1-3.0, and 3.1-4.0, respectively (17).

The threshold of 4.0 ng/mL has been criticized both for not being able to identify cancer (including high-grade) in patients and for encouraging unnecessary prostate biopsies. Establishing a single PSA cut-off for recommending biopsy might be inappropriate. No single value can definitively place men into groups of high and low risk (18). PSA is not diagnostic; it helps assess each man's risk for PC and should be used together with other parameters to decide when a prostate biopsy would be appropriate.

PSA DERIVATIVES

PSA derivatives represent permutations of total PSA that have been tested in clinical practice to improve its sensitivity and specificity. These methods can help identify patients at risk for PC when total PSA (tPSA) does not clearly identify them. The use of PSA derivatives provides a better understanding of an individual's risk, allowing improved detection rates while avoiding unnecessary biopsies.

PSA AND AGE

PSA levels vary through life, but the median PSA level increases over time, mainly after the age of 50, when prostate conditions such as benign prostatic hyperplasia (BPH), prostatitis, and PC become more common. Age-specific PSA reference ranges have been proposed as a means of increasing sensitivity of detection in younger men and specificity in older men. Different thresholds have been established based on the 95th percentile among healthy populations. It was hoped that matching the PSA threshold to the patient's age would avoid unnecessary biopsies and

Table 1 – Sensitivity and specificity of different PSA thresholds.

PSA (ng/mL)	Sensitivity (%)	Specificity (%)
1.1	83.4	38.9
2.1	52.6	72.5
2.6	40.5	81.1
3.1	32.2	86.7
4.1	20.5	93.8
6.1	4.6	98.5
4.1	0.9	99.7

PSA = prostate-specific antigen.

overdetection in older men while diagnosing more instances of cancer in younger men (Table-2). However, further studies, showed that age-specific PSA cutoffs missed 20% to 60% of cancer in men older than 60 years of age (19). Because of this lack of sensitivity, age-specific PSA has not been uniformly accepted.

Studies have indicated that PSA level increases even decades before PC has been diagnosed. Loeb et al. studied 1,178 men in their 40s with risk factors for PC. The risk of subsequent cancer detection was 14.6-fold higher for men with a baseline PSA level between 0.7 and 2.5 ng/mL than for men with levels of < 0.7 ng/mL (20). In a cardiovascular risk assessment study of 21,227 men in Sweden, Lilja et al. showed increased PSA levels up to 20 years before clinical manifestation of advanced disease. Men with PSA 1.01-2.0 ng/mL had a 2.5-fold increased risk of PC compared to men with PSA ≤ 0.5 ng/mL, corresponding to a long-term risk close to the population mean. PSA levels between 2.01-3.0 ng/mL were associated with a 19-fold increased risk of cancer. There was also an increased risk of advanced PC. PSA screening was not widely used in Sweden at the time of this study, thus this population could be used to demonstrate the natural evolution of PC without the interference of PSA screening. The authors suggested that an early PSA test should be done, not for detection of cancer, but to stratify the cancer risk, and for subsequent intervention. Men with PSA > 2.0 ng/mL should be closely followed, while those with PSA below this level should undergo a less frequent follow-up. Such strategy may largely eliminate the poor sensitivity associated with BPH (21).

PSA DENSITY

Although PSA expression is higher in men with BPH, prostate cancer tissue releases more PSA into circulation (22). Volume-based prostate parameters have been evaluated to better interpret PSA levels in men with large prostates.

Patients with BPH have transition zone (TZ) enlargement; most prostate cancers arise in the peripheral zone (PZ). Adjusting PSA to account for TZ volume has been evaluated as a method of distinguishing PC from BPH. Thresholds of 0.23 and 0.38

Table 2 – Age-specific PSA cutoffs.

Age	Normal (ng/mL)
40-49	0-2.5
50-59	3.5
60-69	4.5
70-79	6.5

PSA = prostate-specific antigen.

ng/mL/cm^3 were proposed for TZ volumes above 20 cc and below 20 cc, respectively (23).

PSA density (PSAD) is the serum PSA level divided by prostate volume as assessed by transrectal ultrasound. A direct relationship between PSAD and the risk of cancer was reported by Seaman et al. (24). PSAD cutpoints between 0.10 and 0.18 ng/mL/cc were proposed as the levels that should prompt prostate biopsy. However, using 0.15 ng/mL/cc as the cutoff, Catalona et al. found that half of the cancers detected in men with PSA between 4.0 and 10.0 ng/mL would have been missed. Lower cutpoints appear to maximize sensitivity and specificity. PSAD has also been associated with tumor aggressiveness and treatment outcomes (25).

PSAD is not widely used, as it is an uncomfortable, invasive method requiring skillful performance of transrectal ultra-sonography in which accuracy is influenced by the shape of the prostate. Furthermore, it is more time consuming and expensive than a simple blood test.

PSA VELOCITY AND PSA DOUBLING TIME

The rate at which PSA levels change can help distinguish between patients with BPH and PC. Carter et al. first described this concept, known as PSA velocity (PSAV), in 1992 (26). They measured PSA levels in frozen sera taken from 54 men already participating in a longitudinal study on aging. Long-term serial PSA measurements showed that the men who eventually developed prostate cancer experienced a marked difference in the rate of change years before their diagnosis. PSAV greater than 0.75 ng/mL per

year was significantly associated with PC. This cut-point has shown a 79% sensitivity and 90% specificity in detecting prostate cancer in men with PSA levels between 4.0 and 10.0 ng/mL. Sensitivity, however, dropped to 11% in patients with PSA below 4.0 ng/mL. More recently, cutoffs of 0.1-0.5 ng/mL per year were proposed to recommend prostate biopsy for men within this PSA range (27). As high PSAV is rare when PSA levels are low, further studies are needed to evaluate PSAV cutoff with low PSA levels.

The clinical use of PSAV is limited. Physiological fluctuations in PSA levels and differences in assay standardization compromise its use in the short term. Moreover, recent reports have questioned its role in PC detection. There is little evidence showing that calculation of PSA velocity in untreated patients provides predictive information beyond that provided by absolute PSA level alone (28,29).

PSA doubling time (PSADT) is the time required for PSA to double. It is mostly used to monitor disease progression after radical therapy or as a parameter to decide when patients treated with active surveillance should undergo radical therapy. PSADT has not been shown to be useful in prostate cancer diagnosis.

PSA ISOFORMS

Free PSA and Complexed PSA

PSA exists in several forms. The majority binds to protease inhibitors (mostly ACT) and is known as complexed PSA (cPSA). Approximately 5%-35% of tPSA is not bound and is known as free PSA (fPSA) (30). Current immunoassays can detect both cPSA and fPSA forms in the serum.

The ratio of fPSA to tPSA has been used to increase specificity for PC and to reduce unnecessary biopsies. The proportion of PSA that is complexed to ACT (cPSA) is higher and the percentage of fPSA is correspondingly lower in patients with prostate cancer (31). Thus, the percentage ratio of fPSA (%fPSA) over tPSA is greater in men without PC, and provides additional specificity in detection, as shown by Catalona et al. They reported that in men with tPSA between 4.0 and 10.0 mg/mL, cancer incidence was only 8% if the %fPSA was > 25%; whereas 56% of men were found to have cancer if the %fPSA was less than 10% (Table-3). They also reported that %fPSA > 15% was related to favorable pathological features at radical prostatectomy. They proposed a %fPSA cutoff of 25% as the level at which a prostate biopsy is indicated (32). Further studies also demonstrate the utility of %fPSA. Values varying from 14% to 28% were proposed, which would avoid 20% to 65% of unnecessary prostate biopsies.

The use of %fPSA in men with PSA levels below 4.0 ng/mL remains controversial. In a prospective study of 883 men with PSA levels between 2.0 and 3.9 ng/mL, Raaijmakers et al. showed that only 9% of unnecessary biopsies would be avoided. However, more recent data demonstrated the utility of %fPSA in patients with this PSA range (33). In a group of patients with PSA < 4.0 ng/mL, Djavan et al. showed that a %fPSA cutoff of 27% had a sensitivity of 90% and prevented 18% of unnecessary biopsies (34).

Table 3 – Probability of cancer based on PSA and percentage of free PSA.

PSA (ng/mL)	Probability of Cancer (%)	% free PSA	Probability of Cancer (%)
1.0 - 3.0		< 20	11
4.0 - 10.0	25	0-10	56
		10-15	28
		15-20	20
		20-25	16
		> 25	8

PSA = prostate-specific antigen; % free PSA = percentage of free PSA.

Prostate volume has been shown to influence the %fPSA ratio. Larger prostate in patients with PC is correlated with higher %fPSA (35), detection rates are higher in patients with small prostates. Therefore, different %fPSA were proposed in order to avoid unnecessary biopsies. To maintain 90% sensitivity, a %fPSA of 23% and 14% should be used to indicate a prostate biopsy in prostate of less than or more than 40 cc, respectively (36). This strategy would compensate for the dilution effect caused by large prostates. In men receiving 5α-reductase agents, both tPSA and fPSA levels are decreased and the %fPSA is not altered.

Complexed PSA forms are bound with protease inhibitors, and cPSA serum levels can be determined either by specific assays or by subtracting fPSA from tPSA. Men with prostate cancer have higher levels of cPSA than men without cancer; thus improved specificity of tPSA is suggested. Regarding its clinical use, the 3.2 ng/mL cutoff was estimated to be equivalent to the 4.0 ng/mL tPSA threshold and shows similar diagnostic performance in cancer detection (37). To date, no study has shown superiority of the cPSA or the cPSA/tPSA ratio, compared with %fPSA, to enhance the specificity of prostate cancer detection (38). Despite the fact that, theoretically, cPSA has a small advantage compared to tPSA as a first-line parameter, only the ratio of cPSA to tPSA could reach specificity levels comparable to %fPSA.

Free PSA Isoforms

Free PSA exists as three distinct forms: proPSA, benign PSA (BPSA), and intact PSA (iPSA). ProPSA is an inactive form and is found in increased proportions in patients with PC (39). Mikolajczyk et al. found an overrepresentation of the proPSA (-2) form in serum samples from PC patients compared with BPH samples (40). Catalona et al. showed that use of percentage of proPSA (proPSA/fPSA x 100) improved the specificity of PC detection and decreased the number of unnecessary biopsies in men with tPSA between 2.0 ng/mL and 4.0 ng/mL (41). Others studies have demonstrated that proPSA has enhanced specificity over the use of PSA and %fPSA. However, a recent trial with 2,055 men showed no improvement in accuracy when these forms were compared (42).

BPSA is formed when iPSA is cleaved at amino-acid residues Lys145-146 and Lys182-183, and is present in prostate tissue, serum, and seminal fluid. BPSA has been associated with prostate volume and is highly associated with the transition zone; its levels are increased in patients with BPH. BPSA levels have shown potential for improved distinction of PC from BPH (33). Although it was shown that BPSA represents 0%-60% of fPSA, this measure does not have any clinical use, due to low levels of BPSA in the blood. However, BPSA can be a marker for BPH and may enhance specificity of %fPSA in combination with pro forms of fPSA, or it may be used for therapeutic control of BPH.

Intact PSA is an uncleaved form of PSA, and it is similar to native PSA except it is enzymatically inactive. There are no differences in iPSA levels in men with or without cancer, but the ratio of this marker to fPSA was significantly higher in men with cancer (43). Additional research is under way to determine whether iPSA can improve the accuracy of PC detection, as well as determine if iPSA levels are related to cancer aggressiveness and treatment outcomes.

Even with the development of new assays and discovery of PSA isoforms, there is still no agreement on how best to improve the detection rate in clinical practice. Using a single PSA cutoff is inappropriate because it misses a significant number of cases. Any attempt to improve the detection rate will be subject to a lower specificity. The use of PSA derivatives is not widespread, mainly because among them, only %fPSA ratio alone has proved to be an addition. This scenario indicates the need for a new biomarker that can improve specificity of prostate cancer detection without poor sensitivity.

CONCLUSION

Although PSA is one of the most valuable cancer markers, it is far from perfect. PSA screening can lead to unnecessary biopsies, and overdiagnosis and overtreatment of clinically insignificant prostate cancer. Standard thresholds miss some clinically significant cancer, and no cutoff has reached high

sensitivity while preserving an acceptable specificity. Instead of having a static threshold, PSA levels should be considered as an indicator of risk to be weighted in combination with PSA derivatives, PSA isoforms, and clinical features such as age, ethnicity, and BMI. The combination of these data can be analyzed through multivariate logistic regression models, nomograms, or artificial neural networks, which would calculate each man's risk of having PC. Those with higher risk would undergo prostate biopsy.

Early baseline PSA measurement could be useful in identifying men who are at a higher risk of developing PC in the future, and they can be directed to a more intensive surveillance protocol than men with low risk for cancer. Men with higher levels should be closely followed, while those with normal levels should undergo a less frequent follow-up. This strategy would facilitate a higher rate of diagnosis in younger men while avoiding overdiagnosis in older men.

New markers have been discovered with the help of recent technology, and future studies will demonstrate their usefulness in PC detection. Until then, PSA will remain as the cornerstone of PC screening and detection.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In this review article by Nogueira et al., the authors discuss the diagnostic and therapeutic utility of using serum prostate specific antigen (PSA) in the screening for prostate cancer. The authors highlight many of the merits and drawbacks of using serum PSA as a screening tool. As serum PSA cutoffs prompting prostatic biopsies are lowered, the incidence of a negative prostatic biopsy increases (i.e. the positive predictive value of the biopsy decreases). As well, this results in the overdetection of clinically insignificant prostate cancer which has a low associated risk of local-regional and systemic progression without active treatment. This leads to the ultimate question: How can we identify the patients with prostate cancer at high-risk of progression and then select these patients for risk-appropriate treatment modalities?

In evaluating the utility of a screening tool, several criteria that should be met are: 1) Does the screening test detect the disease before it becomes clinically detectable? 2) Is the test non-invasive and easy to perform in a clinic setting? 3) Does the earlier detection of the disease using this screening tool alter the natural history of the disease? 4) Is the test cost effective? For the most part, PSA meets several of these criteria (namely criteria 1, 2, and 4) however the major hindrance with the test is that although we have clearly noted a stage migration in prostate cancer since integration of serum PSA as a screening tool, it remains unclear and still debated whether there is a survival benefit in screening a patient population with serum PSA. Two large prospective clinical trials were recently published: The Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial by Andriole et al. (1) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) by Schröder et al. (2). These studies have attempted to address this question in U.S. and European patient cohorts, respectively. Although the study design and clinical criteria differed among these two studies, they had very contrasting conclusions in that the PLCO study concluded after 7 to 10 years of follow-up, the death rate of prostate cancer in a PSA screening population did not differ from that in a non-screened patient population whereas in the ERSPC trial, the authors concluded that PSA screening resulted in a reduction in prostate cancer related deaths by 20% but was associated with a high-risk of overdiagnosis. Although the reasons for these significantly differing conclusions in both studies will be argued for many years to come, it remains that at this point in time, we still cannot convincingly demonstrate that there is a clear and definitive survival benefit to using serum PSA as a screening tool. Furthermore, many of our governing bodies and associations will not take a firm position on supporting the role of serum PSA as a screening tool until this survival benefit is convincingly demonstrated.

In those patients currently seeking prostate cancer screening, a combination of digital rectal examination and serum PSA screening currently remains the standard to which other screening tools must be compared. In addition, an evolving view among many urologists and oncologists is that a baseline serum PSA should be obtained in most male patients at the age of 40 years old to help stratify those patients at increased risk of prostate cancer and those best suited for rigorous screening. Similarly, recent reports would suggest that a rapid rise in the serum PSA (greater than 2 ng/mL rise) in the year prior to the diagnosis of prostate cancer helps further define those patients at increased risk of disease-progression and for whom, a high-risk treatment protocol may best be suited.

There are clear limitations to using serum PSA as a screening tool for prostate cancer and new novel tissue, serological, and urinary markers will likely replace PSA in the not too distant future. However, at this time, serum PSA remains the most utilized and useful screening tool in our diagnostic armamentarium. The onus now lies on the scientific community to develop and validate a better screening tool which can identify those patients at increased risk of disease progression and for whom definitive local or multimodal therapy is best suited.

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