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Active Surveillance for Low-Risk Prostate Cancer Worldwide: The PRIAS Study

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Abstract

Background: Overdiagnosis and subsequent overtreatment are important side effects of screening for, and early detection of, prostate cancer (PCa). Active surveillance (AS) is of growing interest as an alternative to radical treatment of low-risk PCa.
Objective: To update our experience in the largest worldwide prospective AS cohort.
Design, setting, and participants: Eligible patients had clinical stage T1/T2 PCa, prostate-specific antigen (PSA) ≤10 ng/ml, PSA density <0.2 ng/ml per milliliter, one or two positive biopsy cores, and Gleason score ≤6. PSA was measured every 3–6 mo, and volume-based repeat biopsies were scheduled after 1, 4, and 7 yr. *Reclassification* was defined as more than two positive cores or Gleason >6 at repeat biopsy. Recommendation for treatment was triggered in case of PSA doubling time <3 yr or reclassification.
Outcome measurements and statistical analysis: Multivariate regression analysis was used to evaluate predictors for reclassification at repeat biopsy. Active therapy–free survival (ATFS) was assessed with a Kaplan-Meier analysis, and Cox regression was used to evaluate the association of clinical characteristics with active therapy over time.
Results and limitations: In total, 2494 patients were included and followed for a median of 1.6 yr. One or more repeat biopsies were performed in 1480 men, of whom 415 men (28%) showed reclassification. Compliance with the first repeat biopsy was estimated to be 81%. During follow-up, 527 patients (21.1%) underwent active therapy. ATFS at 2 yr was 77.3%. The strongest predictors for reclassification and switching to deferred treatment were the number of positive cores (two cores compared with one core) and PSA density. The disease-specific survival rate was 100%. Follow-up was too short to draw definitive conclusions about the safety of AS.
Conclusions: Our short-term data support AS as a feasible strategy to reduce overtreatment. Clinical characteristics and PSA kinetics during follow-up can be used for risk stratification. Strict monitoring is even more essential in men with high-risk features to enable timely recognition of potentially aggressive disease and offer curative intervention. Limitations of using surrogate end points and markers in AS should be recognized.
Trial registration: The current program is registered at the Dutch Trial Register with ID NTR1718 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1718).
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1. Introduction

Prostate cancer (PCa) affects many men worldwide, with >900 000 diagnoses and >258 000 deaths from the disease in 2008 [1]. Studies on PCa screening have shown a positive effect of screening, with a reduction of disease-specific mortality of up to 21–30% [2,3]. However, because of the increasing use of prostate-specific antigen (PSA) testing over the last two to three decades, the proportion of low-risk tumors for which early detection and treatment will not change prognosis has been rising [4]. Treatment of these so-called overdiagnosed cases will inevitably lead to overtreatment and its potential side effects, thereby negatively affecting the patients' quality of life.

Over the last decade, active surveillance (AS) has evolved as an alternative to radical treatment of low-risk PCa. AS focuses on the prevention of overtreatment by selecting patients with low-risk disease features and strictly monitoring them over time to recognize any potential risk reclassification that would justify deferred radical treatment, still with curative intent. Several AS studies have been initiated worldwide that show quite similar and favorable outcomes. However, follow-up in the majority of cohorts is still short, and prospective validation of criteria for selecting low-risk disease therefore is still lacking. In 2006, the Prostate Cancer Research International: Active Surveillance (PRIAS) study was initiated to counteract overtreatment and contribute to prospective data collection. PRIAS aims to reflect daily practice by collecting data from affiliated centers worldwide using an Internet-based decision tool and the PRIAS protocol. The first data on this study were reported on the first 500 patients in 2009 [5]. This study represents an update of our experience with nearly 2500 patients.

2. Methods

The PRIAS study started including patients in December 2006, and recruitment is ongoing. More than 100 medical centers in 17 countries worldwide contribute to the collection of data using an Internet-based tool for entering information on patients' baseline and follow-up characteristics (www.prias-project.org). This report was updated until May 2012. Eligible patients fulfill the PRIAS inclusion criteria for low-risk PCa: clinical stage T1C/T2, PSA ≤10 ng/ml, PSA density (PSA-D) <0.2 ng/ml per milliliter, one or two positive biopsy cores, and Gleason score (GS) ≤6.

The follow-up protocol scheduled PSA measurements every 3 mo for the first 2 yr and PSA measurements every 6 mo thereafter. Repeat biopsies were scheduled after 1, 4, and 7 yr; in case of a PSA doubling time (PSA-DT) between 3 yr and 10 yr, yearly repeat biopsies were advised. Volume-dependent biopsies were recommended according to protocol (prostate volume <40 cm^3: 8 biopsy cores; 40–60 cm^3: 10 biopsy cores; and >60 cm^3: 12 biopsy cores). Risk reclassification at repeat biopsy triggered a recommendation for active treatment and was defined as three or more positive biopsy cores and/or GS >6. PSA-DT was calculated by plotting the base 2 logarithm of the PSA value against time since diagnosis; the doubling time can be calculated as the reciprocal value of the slope of the regression line through these points. PSA-DT <3 yr was used as a recommendation to trigger intervention only after a minimum of four follow-up visits (ie, after 1 yr of follow-up).

Baseline clinical characteristics (age at diagnosis, PSA, PSA-D, clinical T stage, number of biopsy cores, and number of positive cores) and PSA-DT at the time of repeat biopsy were analyzed in a multivariate logistic regression with respect to reclassification at repeat biopsy. PSA-D was calculated as PSA divided by total prostate volume. The odds ratio for PSA-D was reported per 0.10-U increase to facilitate clinical interpretation. Because of small numbers, clinical stage T2 was not further subdivided into specific categories. Kaplan-Meier analysis was used to evaluate active therapy–free survival (ATFS) over time. In addition, time to active treatment was examined with Cox regression analysis to evaluate baseline characteristics associated with switching to deferred therapy. To evaluate longer follow-up in our cohort, we selected a subgroup of patients who had been diagnosed ≥2.5 yr before last follow-up (May 2012) and had been followed on AS for ≥6 mo. Clinical T stage (T1C or T2) and PSA-DT (negative and >10 yr, 3–10 yr, <3 yr) were stratified into groups; other characteristics were used as continuous variables. The p values were calculated using the Mann-Whitney U test (continuous variables) and the χ^2 test (categorical variables). Statistical analyses were performed using SPSS statistical software v.17.0 (IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, with $p < 0.05$ considered to be statistically significant.

3. Results

Up to May 2012, 2494 men (median age: 65.8 yr) meeting all inclusion criteria were included in PRIAS. The distribution across participating countries is shown in Table 1. Median follow-up for the cohort was 1.6 yr (25th and 75th percentile [25–75p]: 1.0–2.8 yr). Baseline characteristics of the study group are shown in Table 2.

A total of 1858 repeat biopsies were performed in 1480 men. A first repeat biopsy was done in 1480 patients (79.7%), 308 patients (16.6%) underwent a second repeat biopsy, 60 patients (3.2%) had three repeat biopsies, and 10 patients (0.5%) received four repeat biopsies. A total of 687 biopsies (37.0%) were negative for PCa, which represented 542 of the first repeat biopsies (36.6%). In total, 415 patients receiving one or more repeat biopsies (28.0%) were reclassified during follow-up; 89 patients (21.4%) demonstrated GS upgrading, 212 patients (51.1%) were reclassified based on the number of positive cores, and 114 patients

Table 1 – Participating countries in the PRIAS study

Country	No. (%)
The Netherlands	1129 (45.3)
Italy	364 (14.6)
Finland	288 (11.5)
Japan	243 (9.7)
Germany	110 (4.4)
France	93 (3.7)
Canada	87 (3.5)
Sweden	57 (2.3)
Spain	46 (1.8)
Australia	36 (1.4)
Norway	17 (0.7)
Czech Republic	12 (0.5)
Austria	8 (0.3)
Switzerland	2 (0.1)
Turkey	1 (0.04)
Belgium	1 (0.04)
New Zealand	0*
Total	2494 (100)

* Only recently joined the PRIAS study.

Table 2 – Patient characteristics at baseline

	All patients, *n* = 2494	No treatment, *n* = 1967	Active treatment, *n* = 527	*p* value
Age, yr, median (25–75p)	65.8 (61.0–70.4)	66.0 (61.1–70.6)	64.9 (60.9–69.8)	0.09
PSA, ng/ml, median (25–75p)	5.6 (4.4–7.0)	5.5 (4.3–7.0)	5.6 (4.6–6.9)	0.51
Prostate volume, median (25–75p)	44 (35–57)	45 (35–58)	41 (34–53)	<0.001
PSA-D, median (25–75p)	0.13 (0.09–0.16)	0.12 (0.09–0.16)	0.14 (0.11–0.17)	<0.001
Cores, no., median (25–75p)	10 (8–12)	10 (8–12)	10 (8–12)	<0.001
Clinical stage, no. (%)				0.09
T1	2122 (85.1)	1692 (86.0)	430 (81.6)	
T2	372 (14.9)	275 (14.0)	97 (18.4)	
T2A	324 (87.1)	240 (87.3)	84 (86.6)	
T2B	34 (9.1)	25 (9.1)	9 (9.3)	
T2C	14 (3.8)	10 (3.6)	4 (4.1)	
Positive cores, no. (%)				<0.001
1	1717 (68.8)	1404 (71.4)	313 (59.4)	
2	777 (31.2)	563 (28.6)	214 (40.6)	

PSA = prostate-specific antigen; PSA-D = prostate-specific antigen density; 25–75p = 25th and 75th percentile.

(27.5%) had a combination of both. Median time to the first repeat biopsy was 1.1 yr (25–75p: 1.0–1.3 yr). Compliance with the first repeat biopsy (defined as undergoing the repeat biopsy within 1.5 yr from initial diagnosis) in men followed for ≥1.5 yr was found to be 81%. Of all 415 patients with an unfavorable repeat biopsy result, 305 patients (73.5%) received active treatment, whereas 110 patients (26.5%) chose to continue on AS despite the protocol recommendation (of these patients, 60% were reclassified based on only number of positive cores, and 40% showed upgrading).

Predictors for reclassification (ie, GS >6 and/or more than two positive cores) on the first repeat biopsy and for any reclassification on repeat biopsy during follow-up are listed in Table 3. PSA-D and the number of positive cores at diagnosis were found to be the most important predictors, while age and baseline PSA value also turned out to be significantly associated with reclassification on repeat biopsy. When PSA-DT at the time of repeat biopsy was added to the analysis, values between 3 yr and 10 yr and, even more so, values <3 yr also showed an association with reclassification.

In total, 1885 patients (75.6%) continued on AS, 527 patients (21.1%) underwent active therapy, 43 patients (1.7%) were lost to follow-up, 21 patients (0.8%) switched to watchful waiting because of increasing comorbidity, and 18 patients (0.7%) died of causes other than PCa. The median time to active therapy was 1.2 yr (25–75p: 1.0–1.6 yr), while the median time free from intervention for the rest of the cohort was 1.9 yr (25–75p: 1.0–3.1 yr). Figure 1 shows the ATFS. The ATFS at 2 yr and 4 yr was 77.3% and 67.7%, respectively.

Of all men undergoing deferred treatment, 387 men (73.4%) had a protocol-based reason to do so; 47 men (8.9%) switched because of anxiety; and 93 men (17.6%) had another reason, such as a solitary PSA increase, urinary symptoms, or patient's preference. Of all patients with

Table 3 – Multivariate analysis of possible predictors for reclassification at repeat biopsy

Baseline characteristics	First repeat biopsy, *n* = 1480		All repeat biopsies, *n* = 1858	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age at diagnosis	1.03 (1.01–1.05)	0.02*	1.02 (1.00–1.04)	0.02*
PSA	0.9 (0.82–0.95)	0.002*	0.9 (0.84–0.96)	0.002*
PSA-D†	3.0 (2.14–4.28)	<0.001*	2.5 (1.87–3.45)	<0.001*
Clinical stage				
T1C	Ref.	Ref.	Ref.	Ref.
T2	1.3 (0.92–1.80)	0.14	1.1 (0.81–1.49)	0.56
Total biopsy cores	1.0 (0.90–1.00)	0.05	1.0 (0.92–1.00)	0.07
Positive cores				
1	Ref.	Ref.	Ref.	Ref.
2	2.2 (1.67–2.81)	<0.001*	2.1 (1.69–2.69)	<0.001*
PSA-DT**				
Negative or >10 yr	Ref.	Ref.	Ref.	Ref.
3–10 yr	1.3 (0.93–1.70)	0.14	1.3 (1.01–1.70)	0.04*
<3 yr	1.6 (1.20–2.25)	0.002*	1.7 (1.27–2.29)	<0.001*

OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen; PSA-D = prostate-specific antigen density; Ref. = reference group; PSA-DT = prostate-specific antigen doubling time.

† OR for PSA-D is reported per 0.10-U increase.

* Significant results ($p < 0.05$).

** A separate analysis was performed with PSA-DT added to the baseline characteristics; the significance of the other outcomes remained unchanged.

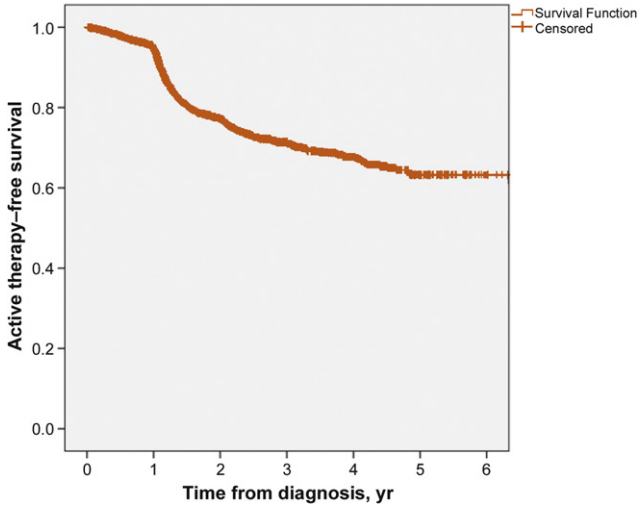

Fig. 1 – Active therapy–free survival over time.

Table 5 – Association of baseline characteristics with deferred active treatment over time

Baseline characteristics	Deferred active therapy, $n = 527$	
	HR (95% CI)	p value
Age at diagnosis	1.0 (0.98–1.01)	0.62
PSA	1.0 (0.92–1.02)	0.22
PSA-D†	2.1 (1.68–2.70)	<0.001*
Clinical stage		
T1C	Ref.	Ref.
T2	1.1 (0.86–1.34)	0.55
Total biopsy cores	0.95 (0.91–0.98)	0.002*
Positive cores		
1	Ref.	Ref.
2	1.7 (1.43–2.04)	<0.001*

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; PSA-D = prostate-specific antigen density; Ref = reference group.
† HR for PSA-D is reported per 0.10-U increase.
* Significant results ($p < 0.05$).

protocol-based reasons, 79% were biopsy-related, whereas the remaining 21% of patients had a PSA-DT <3 yr (Table 4). Cox analysis showed PSA-D, the number of positive cores (two compared with one), and the total number of cores at baseline to be predictive for the likelihood of being switched to active treatment during follow-up (Table 5). The majority of patients underwent radical prostatectomy or radiotherapy as deferred treatment in quite evenly distributed amounts (Table 4), 8 men switched to hormonal therapy, 4 men received high-intensity focused ultrasound, and in 24 other men the type of final therapy was unknown. The outcomes of 167 men undergoing radical prostatectomy after initial surveillance within the study were recently published [6]. A separate report on radiotherapy results will be the subject of a subsequent manuscript. There have been no PCa deaths in our cohort; however, two cases of metastatic disease were reported. The overall survival at 2 yr and 4 yr was 97.1% and 86.5%, respectively.

In all, 1071 patients were eligible for the evaluation of longer follow-up in our cohort. Median follow-up was 3.1 yr (1.8–4.0 yr). This subgroup showed results that were very similar to the results in the complete cohort regarding baseline characteristics, reclassification on repeat biopsy (25%), predictors for reclassification and active treatment, and ATFS at 2 yr (76%) and 4 yr (66%).

Table 4 – Type of and reason for deferred therapy in 527 treated patients

Treatment type	No. (%)
Radical prostatectomy	253 (48.0)
Radiotherapy	238 (45.2)
Hormonal therapy	8 (1.5)
Other* or unknown therapy	28 (5.3)
Reason for treatment	
Protocol-based	387 (73.4)
Gleason score >6**	61 (15.8)
More than two positive cores	146 (37.7)
Gleason score >6 and more than two positive cores	99 (25.6)
PSA-DT <3 yr	81 (20.9)
Anxiety	47 (8.9)
Other***	93 (17.6)

* Four patients received high-intensity focused ultrasound therapy.
** One patient was reclassified after review of the specimen from a prediagnostic transurethral resection of the prostate.
*** Other reasons included increase in PSA with PSA-DT >3 yr, lower urinary tract symptoms, patient's wish, and unknown reasons.

4. Discussion

We report updated results from the largest prospective AS cohort for low-risk PCa that acquires data from >100 medical centers worldwide. Our analyses show that in addition to age and PSA at diagnosis, both PSA-D and the number of positive cores at diagnosis (two compared with one) are important predictors for reclassification at repeat biopsy. The latter two predictors are also shown to be associated with the likelihood of switching to active therapy during follow-up. The majority of patients remained free from therapy, and it is important to note that while 18 men died from other causes, no patients died from PCa.

As a response to increasing overdiagnosis and subsequent overtreatment, several AS studies have been initiated worldwide [7–11]. Our data are consistent with the data previously reported regarding reclassification, ATFS, and favorable disease-specific outcomes [7–11]. Although follow-up in most cohorts is still relatively short, it has been shown that this alternative management strategy for carefully selected patients is associated with a disease-specific mortality of <3% at 10 yr [7]. It was found that AS was associated with the greatest quality-adjusted life expectancy when compared with active treatment of low-risk PCa [12]. These data reinforce the use of AS as an alternative to the radical treatment of favorable-risk, localized PCa. Our results for data with longer follow-up (median: 3.1 yr) are similar to our results with relatively short follow-up.

In our cohort, active therapy was triggered by a protocol-based reason in 73.4% of patients; the majority of these patients had biopsy-related reasons, and 20.9% of the patients switched because of short PSA-DT. PSA kinetics are not used as a trigger for intervention in all AS series [9–11]. In the long-term follow-up series described by Klotz et al. [7], PSA-DT was used to identify patients for definitive therapy. The results also showed an 8.5-fold greater risk of PSA progression after active therapy in men with a PSA-DT <3 yr compared with men with longer PSA-DT, indicating the relevance of PSA-DT as a marker for more aggressive disease.

However, defining the exact triggers for deferred intervention, as well as selecting favorable-risk disease at diagnosis, remains difficult in the absence of hard end points such as PCa mortality. As yet, GS might be one of the most important predictors for disease-specific outcome [13,14]. However, although GS 6 is considered to represent low-risk disease, it is important to note that this classification is not as clear-cut, and not all patients harboring Gleason 3 + 4 disease will be better off receiving radical therapy [15]. The number of positive cores used as a proxy for tumor volume, as described by Stamey et al. [16] and Epstein et al. [17], is another point of debate, since the effect of tumor volume on PCa outcome has been discussed, and several studies have shown no independent predictive value [18,19]. Also, a recent study [20] showed that the PCa volume threshold for insignificant disease is 1.3 ml, which is more than twice as high as the 0.5 ml originally described by Stamey et al. [16]. This finding implies that a cutoff of two positive cores to define low-risk disease might be too restrictive, and additional research is necessary to focus on adjusting and extending AS criteria regarding histologic features of the disease without compromising the window of opportunity for cure.

In total, 27% of the cohort experienced disease reclassification at repeat biopsy during follow-up. We know that prostate biopsies are subject to misclassification, which was previously demonstrated by the levels of reclassification at repeat biopsy [21] and radical prostatectomy [6] in our AS cohort. Regarding the protracted course of PCa, especially in low-risk disease [22], this phenomenon is very likely attributable to initial misclassification instead of true disease progression. It is hoped that in the future, better markers and imaging modalities, such as multiparametric magnetic resonance imaging (MRI), will contribute to more accurate staging and grading. For now, repeat biopsies are vital to either confirm favorable-risk disease or recognize potential aggressive disease in time to preserve a good prognosis. Our data show that the protocol is not always strictly followed, which resulted in skipping scheduled repeat biopsies in approximately 19% of the cases. Moreover, we found that one-quarter of patients continue on AS despite a biopsy-based recommendation for active therapy. These observations should alert treating physicians, especially in the presence of clinical characteristics predicting adverse features and potentially aggressive disease, to urge patients to follow a strict monitoring protocol.

The strongest predictors for reclassification at repeat biopsy in our cohort were the number of positive cores and PSA-D, which correspond to a previous report we published on 757 first repeat biopsies [21]. When we evaluated GS upgrading as the single outcome of unfavorable repeat biopsy, we found that these predictors, including PSA-DT <3 yr, maintained their significant association (data not shown).

We found the same baseline characteristics to be associated with switching to active therapy over time. Since the number of positive cores is also a trigger for intervention, it might be expected that this factor would play a role in the likelihood of eventually undergoing treatment in our series. On the contrary, PSA-D seems to be an important independent predictor for adverse findings, which has repeatedly been shown in other studies on histologic disease progression on repeat biopsy [23–25]. Also, PSA-D was found to be predictive of insignificant PCa at radical prostatectomy [26,27]. This observation is debated in the literature: Smaller prostates are associated with more aggressive disease [28,29]; however, this observation could also be attributable to PSA performance characteristics [30]. Other factors such as BMI and ethnicity could potentially influence PCa prognosis, but data on these factors are lacking in our cohort.

Although we observed a 100% disease-specific survival, longer follow-up clearly is needed to answer the question of the impact of AS on survival, also given the relatively high overall survival rate in our cohort. We know from screening trials that even 10 yr is too short to evaluate PCa mortality [2], which holds even more for patients who are considered low-risk and usually have longer life expectancies. It is hoped that with longer follow-up, we will be able to improve the strategy of AS by increasing its availability in a safe way and thereby preventing, or at least delaying, overtreatment in as many patients as possible.

Ongoing research efforts must focus on improving selection for AS and early identification of occult high-risk PCa. New markers and imaging modalities such as MRI seem promising, but more work is needed to evaluate them in an AS setting. Immediate repeat biopsies, as well as template- and MRI-guided biopsies, might help to improve patient classification; however, an important caveat in AS remains the lack of validated measures of outcome. The indicators of risk reclassification that are currently used as a surrogate for outcome in most AS programs still require further study, to which our prospective AS data can hopefully contribute with longer follow-up.

5. Conclusions

In an era of widespread availability of PSA-based screening, AS is of growing interest as an alternative to treatment of low-risk PCa. PRIAS is the largest observational prospective study evaluating AS worldwide and our data support AS as a feasible strategy to reduce overtreatment, at least in the short term, without compromising curability.

Clinical characteristics and PSA kinetics can be used to predict who will be reclassified to higher risk during

follow-up and who is more likely to switch to deferred active therapy over time. Caution is warranted in patients harboring these higher-risk features, and strict monitoring of the histologic and biochemical features is essential. The limitations of predicting the outcome of PCa using surrogate end points and markers should be recognized. Nonetheless, the majority of patients in this study remain free from any therapy and adverse events are rare, although follow-up is still too short to draw definitive conclusions.

Author contributions: Meelan Bul had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bul.
Acquisition of data: Bul, Valdagni, Pickles, Kakehi, Rannikko, Bjartell, van der Schoot, Cornel, Conti, Boevé, Staerman, Vis-Maters, Vergunst, Jaspars, Strölin, Schröder, Bangma.
Analysis and interpretation of data: Bul, Zhu.
Drafting of the manuscript: Bul.
Critical revision of the manuscript for important intellectual content: Bul, Zhu, Valdagni, Pickles, Kakehi, Bjartell, van der Schoot, Cornel, Conti, Schröder, Bangma, Roobol.
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Supervision: Bangma, Roobol.
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