

# Multiparametric magnetic resonance imaging-transrectal ultrasound-guided cognitive fusion biopsy of the prostate: Clinically significant cancer detection rates stratified by the Prostate Imaging and Data Reporting System version 2 assessment categories

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Cite as: *Can Urol Assoc J* 2018;12(12):401-6. <http://dx.doi.org/10.5489/cuaj.5254>

Published online June 19, 2018

## Abstract

**Introduction:** We aimed to report the clinically significant prostate cancer (PCa) detection rate in men undergoing magnetic resonance imaging-transrectal ultrasound (MRI-TRUS)-cognitive fusion (CF) targeted biopsies stratified by the Prostate Imaging and Data Reporting System (PI-RADS) version 2 (v2) scores.

**Methods:** With a quality assurance waiver from the institutional review board, we identified a cohort of men who underwent MRI-TRUS-CF and synchronous template biopsy from 2015–2017. MRI (PI-RADS v2 score, lesion size, lesion location [peripheral or transition zone (PZ/TZ)]), and CF-TRUS biopsy (operator experience, TRUS visibility, and number of biopsies) features were extracted. The primary outcome was diagnosis of clinically significant (Gleason score  $\geq 3+4=7$  or International Society of Urological Pathology [ISUP] grade group  $\geq 2$ ) PCa.

**Results:** During the study period, 131 men (with 142 PI-RADS v2 score  $\geq 3$  lesions) met inclusion criteria; 98 men had previously negative template biopsy and 33 were on active surveillance for previously detected low-grade PCa. In total, 41.9% (55/131) men had clinically significant PCa — 17.6% (23/131) detected on targeted biopsy only, 8.4% (11/131) on template biopsy only, and 16.0% (21/131) on both targeted and template biopsy. Clinically significant PCa detection stratified by PI-RADS v2 scores were: 11.1% (3/27) for score 3 (indeterminate), 42.9% (24/56) for score 4 (significant cancer likely), and 35.6% (21/59) for score 5 (significant cancer very likely). Clinically significant PCa detection rates in targeted biopsies were better among PZ (41.8% [33/79]) compared to TZ (23.8% [15/63]) lesions ( $p=0.025$ ) in TRUS-visible lesions ( $p=0.033$ ) and in the most experienced radiologists ( $p=0.05$ ), with no difference by lesion size or number of additional core biopsies performed (all  $p>0.05$ ).

**Conclusions:** CF-MRI-TRUS-guided targeted biopsy yielded substantially lower rates of clinically significant cancer in PI-RADS v2

score 4 and 5 lesions when compared to published results using in-bore MR-guided or automated MRI-TRUS fusion guidance systems. Cancer detection was worst for TZ lesions.

## Introduction

Multiparametric (mp) prostate magnetic resonance imaging (MRI) (the combination of anatomic T2-weighted imaging with functional imaging techniques [diffusion-weighted imaging and dynamic contrast-enhanced MRI]) is the reference standard test for imaging the prostate.<sup>1</sup> Multiparametric MRI is accurate for detection of clinically significant prostate cancer (PCa), defined on imaging studies as Gleason score  $\geq 3+4=7$  tumour measuring  $\geq 0.5$  mL in size.<sup>2</sup> Multiparametric MRI is particularly valuable for detection of tumours located anterior to the urethra (in the anterior horns of the peripheral zone [PZ] and in the transition zone [TZ]), areas that are undersampled or not sampled at all during template transrectal ultrasound (TRUS)-guided biopsy.<sup>3</sup> Multiparametric MRI is increasingly being used during active surveillance (AS) for men with low-volume, low-grade (Gleason score  $3+3=6$ ) PCa with discordant clinical findings<sup>4,5</sup> and in men with previously negative template biopsies and high clinical suspicion of PCa.<sup>6</sup> It has a proven value in biopsy-naïve men, although the data in this patient population, particularly in Canada, remains immature.<sup>6</sup>

While mpMRI has been widely adopted by urologists in Canada and is now a fundamental component of PCa management, improving diagnosis of cancers that may be occult on template biopsy, has also created new challenges. Lesions detected on mpMRI require targeted biopsy to be confirmed as histologically representing clinically significant PCa and to better inform management decisions. Histological confirmation is helpful because false positive MRI interpretations can occur<sup>7</sup> and because not all lesions detected on mpMRI have

the same probability of representing significant PCa. In 2015, the Prostate Imaging and Data Reporting System (PI-RADS) version 2 (v2) document was released to standardize reporting of prostate mpMRI and provide urologists and other physicians managing PCa with a probability scale (from 1–5) of how likely a lesion detected on mpMRI represents significant PCa.<sup>1,8</sup> A PI-RADSv2 score of 4 or 5 typically warrants targeted biopsy due to “likely” and “very likely” probability scores of clinically significant PCa.<sup>1,8</sup>

Targeted biopsy of mpMRI-detected lesions can be performed in-bore (i.e., within the MRI suite using MRI guidance), through advanced automated fusion of mpMRI data onto real time three-dimensional (3D) TRUS images, or through cognitive fusion (CF) of mp-MRI and 2D TRUS (where an operator mentally fuses MRI and TRUS images while performing biopsies).<sup>9</sup> A recent meta-analysis showed equivalently significant PCa detection rates for in-bore MR-guided and automated MRI-TRUS fusion-guided biopsies, both of which outperformed CF; however, reporting of MRI among included studies predated PI-RADS v2.<sup>10</sup> In a previous Canadian study, Cool et al demonstrated that automated MRI-TRUS fusion was superior to CF for PCa detection even among experienced operators;<sup>11</sup> however, similarly, this study was published in the era before PI-RADS v2, which may have resulted in more false negative MRI interpretations and makes comparison to other studies reporting PCa detection with targeted biopsy difficult. The purpose of the present study is to report the rates of clinically significant PCa detection using mpMRI-TRUS-CF biopsies in men with mpMRI-detected lesions stratified by PI-RADS v2 score from a single institution tertiary care referral centre for PCa, and to evaluate factors that may influence significant PCa detection at CF biopsy.

## Methods

### Patient selection and mpMRI

With a quality assurance waiver from the institutional review board, we performed a search using our institutional Picture Archiving and Data Reporting System (PACS; Horizon Medical Imaging, McKesson corporation, San Francisco, CA, U.S.) to identify all patients who underwent CF MRI-TRUS-guided biopsy of the prostate between January 2015 and June 2017. We identified 236 patients and excluded 13 men in whom targeted biopsy was performed due to suspicion of locally recurrent tumour after radical prostatectomy (RP) or radiotherapy. Of the 223 remaining patients, all mpMRI examinations were reviewed by an expert genitourinary (GU) radiologist (NS) with 13 years of experience in prostate mpMRI, having interpreted over 500 prostate mpMRI examinations using PI-RADS v2. The radiologist also serves

as the Director of Prostate Imaging at our institution. The radiologist was blinded to patient information, including results from CF biopsy and original MRI reports.

After dedicated review, 92 patients were further excluded because: mpMRI was degraded by severe image artifact (n=4), examinations were re-interpreted as negative (PI-RADS v2 score 1 or 2, n=67), examinations were considered positive (PI-RADS v2 score  $\geq 3$ ) but in a discrepant location from the initial interpretation (with the new lesion identified after secondary review not having been sampled at time of biopsy, n=11), or examinations were performed at 1.5 Tesla due to a contraindication to imaging at 3 Tesla (n=10). From the 131 remaining patients, 142 lesions were identified with PI-RADS v2 assessment categories  $\geq 3$  that underwent targeted biopsy. PI-RADS v2 category, maximum size of lesion (measured on transverse axial T2-weighted images), and location of lesions (PZ; base, middle gland, and apex] or TZ) were recorded. All mpMRI examinations were performed on a clinical 3 Tesla MRI system (Discovery 750W, General Electric Medical, Milwaukee, WI, U.S.) using integrated body array coils (endorectal coil was not used) and with sequence parameters compliant with PI-RADS v2<sup>1,8</sup> as described previously.<sup>12–17</sup>

### mpMRI TRUS-guided CF-targeted biopsy and histopathology results

Targeted biopsies were performed using TRUS guidance with CF of mpMRI data onto real time 2D TRUS images. All ultrasound examinations were performed using modern ultrasound equipment (Aloka Prosound Alpha 10, Aloka Hitachi Medical or General Electric Logiq E9, General Electric Healthcare) using endoluminal 4–8 MHz end-fire probes. All biopsies were performed by fellowship-trained abdominal radiologists. During the time period of the study, 12 radiologists performed at least one biopsy, with a mean number of biopsies of 4 $\pm$ 3 (interquartile range [IQR] 2–5). Our CF biopsy program started in January of 2014; however, we included only patients who received biopsy in January 2015 and later to ensure there was an adequate learning period for radiologists performing MRI-TRUS-CF biopsies and because standardized reporting of the CF biopsy procedure (containing information used in this study) was instituted in 2015. Among the 12 radiologists performing targeted biopsies, five radiologists comprising the majority of the prostate biopsy service performed 91.5% (130/142) biopsies (range 16–37 biopsies per radiologist) compared to the other seven, who performed only 8.5% (12/142) biopsies (range 1–2 biopsies per radiologist).

The TRUS-guided biopsy system used for all biopsies employed an 18-gauge, side-cutting needle. All of our biopsy suites are equipped with monitors that enable display of mpMRI, which can be reviewed before or during the biopsy procedure. In 90.8% (119/131) of men, anesthesia was provided using 1% lidocaine nerve block, whereas in

the remaining 9.2% (12/131), anesthesia was provided using both a 1% lidocaine nerve block and conscious sedation. A fleet enema was prescribed prior to the procedure and antibiotic prophylaxis was prescribed to prevent infection, as described previously.<sup>18</sup> In 97.9% (128/131) of men, at time of targeted biopsy a simultaneous extended sextant template biopsy of the PZ was also performed, including 12 biopsies (two each from the bilateral base, middle, and apical portions of the PZ) in accordance with provincial standards for PCa diagnosis. Core-needle biopsy specimens are submitted for laboratory processing and interpretation in separate pathology specimen containers according to the site of sampling. Tissue from biopsy specimens are fixed overnight in 10% neutral buffered formalin. Three histological slides are prepared from each block, each with three serial sections cut at 3µm in thickness and stained with hematoxylin and eosin (H&E). Biopsy results are reported for each core specimen individually.

The CF-TRUS-guided biopsy reports used at our institution employ a mandatory standardized reporting template that specifies the operator, the number of core biopsies performed per target, and whether the mpMRI-detected target was visible on TRUS. These variables were recorded by an abdominal radiology fellow (SJ). The radiology fellow also retrieved the biopsy results from the patient electronic medical record. The presence of cancer at a biopsy site (targeted or template) was recorded by the radiology fellow (SJ), who also recorded the individual Gleason score from core-needle biopsy specimens at each biopsy site. A Gleason score of  $\geq 3+4=7$  was considered clinically significant in this study. In this way, a biopsy result for each targeted lesion, as well as the remainder of the PZ for men who underwent template biopsy at time of fusion biopsy was recorded.

### Statistical analysis

The proportion of detection of all cancers on a per-patient and per-lesion basis was tabulated; however, for all further comparisons, only clinically significant cancers were considered. Clinically significant cancer detection rates were

compared by lesion PI-RADS v2 score, size on MRI, and location on MRI, as well as operator experience, TRUS visibility, and number of core biopsies performed per lesion. Comparisons were performed using independent t-tests, Chi-squared, and logistic regression for multivariable analyses. Statistical analyses were performed using STATA version 13.0 (Statacorp, College Station, T, U.S.) and p values <0.05 were considered statistically significant.

### Results

During the study period, 131 patients having 142 lesions with PI-RADS v2 assessment categories  $\geq 3$  who met the inclusion criteria underwent targeted biopsy. Mean patient age was  $66 \pm 8.2$  years (range 48–86) and mean prostate-specific antigen (PSA) was  $12.8 \pm 11.3$  ng/mL (range 2.1–64). In total, a diagnosis of any PCa, including Gleason score  $3+3=6$  tumours, was established in 74.8% (98/131) of men. When excluding Gleason score  $3+3=6$  PCa, clinically significant cancers were diagnosed in 41.9% (55/131) of men, with 17.6% (23/131) diagnosed on targeted biopsy only, 8.4% (11/131) diagnosed on simultaneous template biopsies only, and 16.0% (21/131) diagnosed on both targeted and template biopsies in the same patient.

Cancer detection rates on targeted biopsies stratified by PI-RADS v2 assessment category are provided in Table 1. From 142 lesions, PI-RADS v2 assessment categories were: score 3 in 19.0% (27/142), score 4 in 39.4% (56/142), and score 5 in 41.5% (59/142). The detection rates of any cancer, including Gleason score  $3+3=6$  cancers, by PI-RADS v2 scores were: 40.7% (11/27) score 3, 67.9% (38/56) score 4, and 69.5% (41/59) score 5. The detection rates of clinically significant cancer by PI-RADS v2 scores were: 11.1% (3/27) score 3, 42.9% (24/56) score 4, and 35.6% (21/59) score 5. There were significantly higher clinically significant cancers detected in score 4 and 5 lesions compared to score 3 lesions ( $p=0.015$ ).

Lesions in the PZ ( $n=79$ ) were associated with a higher rate of clinically significant cancer detection when compared to those located in the TZ ( $n=63$ ) on targeted biopsy

**Table 1. Prostate cancer detection in 142 lesions in 131 men stratified by PI-RADS v2 assessment category and location among targeted biopsies performed using CF of MRI and TRUS**

	PI-RADS v2 assessment category* 3 (n=27)		PI-RADS v2 assessment category 4 (n=56)		PI-RADS v2 assessment category 5 (n=59)	
	PZ (n=23)	TZ (n=4)	PZ (n=35)	TZ (n=21)	PZ (n=24)	TZ (n=35)
Any cancer diagnosis (including Gleason score $3+3=6$ or higher)	30.4% (7/23)	25.0% (1/4)	60.0% (21/35)	66.7% (14/21)	70.8% (17/24)	57.1% (20/35)
Clinically significant cancer (Gleason score $\geq 3+4=7$ )	13.0% (3/23)	0	34.3% (12/35)	19.0% (4/21)	50.0% (12/24)	25.7% (9/35)
No cancer diagnosed	69.6% (16/23)	75.0% (3/4)	40.0% (14/35)	33.3% (7/21)	29.2% (7/21)	42.9% (15/35)

\*PI-RADS version 2 assessment categories were assigned by an experienced radiologist where assessment category 3=likelihood of clinically significant cancer is indeterminate or equivocal, 4=likelihood of clinically significant is high, and 5=likelihood of clinically significant cancer is very high. MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging and Data Reporting System; PZ: peripheral zone; TZ: transition zone; TRUS: transrectal ultrasound.

(41.8% [33/79] vs. 23.8% [15/63];  $p=0.004$ ). PI-RADS v2 score 5 lesions were more frequent in the TZ compared to score 4 lesions (60.7% [34/56] vs. 25.4% [15/59];  $p=0.003$ ). Therefore, we performed subgroup analyses comparing clinically significant cancer detection rates among PI-RADS v2 score 4 and 5 lesions by location in the PZ and TZ. When controlling for zone location, there was no difference in clinically significant cancer detection rates in PI-RADS v2 score 4 vs. 5 lesions in the PZ (score 4: 34.3% [12/35] cancers vs. score 5: 50.0% [12/24];  $p=0.34$ ) or the TZ (score 4: 19.0% [4/21] vs. score 5: 25.7% [9/35];  $p=0.56$ ).

Mean lesion size was  $16\pm 8$  mm (range 5–38), with no difference in detection of clinically significant cancers by lesion size ( $p=0.84$ ). There was a significantly higher clinically significant cancer detection rate among targeted biopsies performed by the core radiologists comprising the prostate biopsy service (36.2% [47/130]) compared to the other radiologists who performed targeted biopsies during the study period (8.3% [1/12]) ( $p=0.05$ ). The mean number of core biopsies per lesion was  $2\pm 2$  (range 1–10), with no association between cancer detection and number of biopsies ( $p=0.28$ ). TRUS-visible tumours (47.9% [68/142]) were associated with a higher yield of clinically significant cancer detection (42.6% [29/68] clinically significant cancer detection among TRUS-visible lesions vs. 25.7% [19/74] clinically significant cancer detection among TRUS-non-visible lesions;  $p=0.033$ ) and were associated a higher PI-RADS v2 score ( $p=0.035$ ) and higher Gleason scores ( $p=0.042$ ), but TRUS visibility was not associated with lesion location ( $p=0.78$ ) or size ( $p=0.27$ ).

Followup of the 70 men with PI-RADS v2 score 4 or 5 lesions on mpMRI with biopsies negative for clinically significant cancers was available in only a limited number of patients due to the relatively short period of time between analysis of results and time of biopsy. Two-year followup was available in 17 patients, one-year followup in 27 patients, and in the remaining 26 patients followup was less than one year in duration. For those patients with at least one year of followup: 20.5% (9/44) were subsequently diagnosed with Gleason score 3+4=7 PCa (one on repeat biopsy and eight at RP), 4.5% (2/4) were diagnosed with Gleason score 4+3=7 PCa (both on repeat biopsy), 4.5% (2/44) were diagnosed with large-volume Gleason score 3+3 after RP, 4.5% (2/44) were treated with radiotherapy, 59.0% (26/44) were placed on or remained on AS, and 6.8% (3/44) were discharged from care. In patients with less than one year of followup, no repeat biopsies or other interventions had been initiated at time of data analysis.

## Discussion

This study reports the clinically significant PCa detection rates in mpMRI-TRUS-guided CF biopsies stratified by PI-RADS v2 assessment categories. We observed a low rate of clinically

significant cancer detection in biopsies performed for PI-RADS v2 assessment category 4 (clinically significant cancer likely to be present) and 5 (clinically significant cancer very likely to be present), particularly for lesions located in the TZ. Cancer detection was highest in PZ lesions, those which were TRUS-visible, and when biopsies were performed by the most experienced operators, but did not depend on number of core biopsies performed or lesion size.

The clinically significant cancer detection rates in our study are generally lower than what has been reported for PI-RADS v2 assessment category 4 and particularly for category 5 lesions in previous work using either in-bore or automated MRI-TRUS fusion techniques, which range from 30–78% for PI-RADS v2 score 4 and 78–100% for PI-RADS v2 score 5 lesions.<sup>19–22</sup> Moreover, although followup was only available for patients with a negative targeted biopsy in a minority of men in our cohort, the majority of those who went on to repeat biopsy or definitive treatment had clinically significant cancers diagnosed, suggesting that the discord between MRI interpretation and cognitive biopsy result is due to sampling errors at biopsy and not errors in MRI interpretation. In a previous study by Costa et al, repeated MRI-TRUS automated fusion biopsy in Likert score 5 prostate lesions after an initial round of negative targeted biopsies identified clinically significant cancers in approximately 40% more patients.<sup>23</sup>

A prior meta-analysis performed by Wegelin et al (albeit published before reporting of MRI using PI-RADS v2) demonstrated that CF is inferior to both in-bore and automated MRI-TRUS fusion systems.<sup>10</sup> Our results, the first to show Canadian data for clinically significant PCa detection in mpMRI-detected targets using CF-TRUS-guided biopsies where targets are stratified by the PI-RADS v2 system, confirms results from prior studies, which show that CF is inferior to in-bore MRI-guided or MRI-TRUS automated fusion-guided systems for targeted prostate biopsies. Limitations in detection of clinically significant cancer among PI-RADS v2 score 4 and 5 lesions with CF biopsy are important and must be appreciated by physicians treating PCa and acknowledged by healthcare facilities and funding organizations.

We demonstrated that clinically significant cancer detection rates were particularly low in TZ compared to PZ lesions. This is also an expected observation since TZ lesions are located anteriorly, which is further away from the end-firing TRUS probe and lesion visibility decreases as a function of distance from end-firing endoluminal probes.<sup>3</sup> Not surprisingly, TZ lesions were less TRUS-visible in our study compared to PZ lesions, and TRUS visibility was significantly associated with clinically significant cancer detection. The disproportionately higher number of TZ lesions in our study likely reflects bias due to the population studied (i.e., men with previously negative template biopsy but with persistent clinical suspicion of cancer and those on AS).

TRUS-visible lesions were more likely to be associated with a higher PI-RADS v2 score and higher Gleason scores, which is concordant with what has been reported previously.<sup>24</sup> Our overall yield for clinically significant cancers in PI-RADS v2 score 4 or 5 lesions is comparable to the study by Lai et al, which evaluated cognitive MRI-TRUS fusion in lesions stratified by PI-RADS v2 scores,<sup>25</sup> and our rates of TZ lesions alone is comparable to the study by Murphy et al, which showed clinically significant cancer detection in only one-third of anterior targets using CF.<sup>26</sup>

In our study, there was a significantly higher cancer detection rate in the most experienced compared to the least experienced operators. An often-cited limitation of CF biopsy is operator experience and our results support that targeted biopsies performed using CF have a higher yield among the most experienced operators. There was no difference in cancer detection by number of core biopsies performed in our study. Most studies performing targeted biopsy of mpMRI-detected lesions report a mean number of core biopsies per target of two,<sup>19-21</sup> which is concordant with our data. Increasing the number of biopsies did not improve cancer detection rates in our study, which is an expected outcome since our results indicate that if the lesion is TRUS-visible, it can be effectively sampled, whereas if it is not TRUS-visible, increasing the number of biopsies does not improve the yield of cancer detection. Though an increased number of biopsies is not associated with increased risk of infection, it has been associated with increased patient morbidity, with associations between increased number of biopsies performed and increased post-procedural bleeding and pain.<sup>27</sup> Our study showed decreased clinically significant PCa detection rates in TZ compared to PZ lesions and no difference in PCa detection by CF in larger compared to smaller tumours, which is concordant with the prior results reported by Cool et al.<sup>11</sup>

Our study has limitations. The patient population all underwent their targeted biopsies fairly recently (within three years of data collection and analysis), which limited our ability to perform meaningful long-term followup of patients with PI-RADS score 4 or 5 lesions and negative biopsy. This limitation is expected given that targeted biopsies of MRI-detected lesions have only recently become a part of the standard of care management pathways for men treated with AS or with negative template biopsies and persistent suspicion of cancer. In our study, a majority of these men were either enrolled in or remained on AS and clinically significant cancer diagnosis was established only in a minority of these men during followup.

## Conclusion

We observed a low rate of clinically significant PCa diagnosed on CF mpMRI TRUS-guided biopsy in PI-RADS v2

category 4 and 5 lesions compared to rates of cancer detection reported in the literature using either in-bore or automated MRI-TRUS fusion systems, particularly in TZ tumours. Our lower rates of clinically significant cancer detection are comparable to rates described by other authors using CF as a method of guiding targeted prostate biopsies. There was improved detection of significant cancers in TRUS-visible and PZ lesions, and in the most experienced operators, but no difference in yield by number of additional core biopsies performed or tumour size.

Our results have several important implications for delivery of patient care in Canada. Firstly, when combined with the other Canadian study by Cool et al,<sup>11</sup> it can be concluded that cognitive MRI-TRUS-guided targeted biopsy is not as accurate for sampling of MRI-detected lesions compared to other targeting systems and yields lower than expected rates of significant cancers when MRI findings are stratified by PI-RADS v2. Canadian healthcare facilities and governments must invest capital for the acquisition of alternative targeting systems (e.g., automated MRI-TRUS fusion systems or in-bore MRI-directed guidance systems) to maintain accuracy of PCa diagnosis compared to other developed countries. Secondly, when an MRI-detected lesion is not TRUS-visible, a physician receiving targeted biopsy results should be aware of the low cancer detection rates from CF, particularly in TZ lesions. Negative cognitive biopsy results in this setting should not be considered as truth and level of suspicion of cancer based upon MRI results (e.g., PI-RADS score) and other clinical parameters should guide management decisions for patients. Third, increasing the number of core biopsies to sample a target that is not TRUS-visible did not improve yield in our study and we suggest that no more than 2–3 targeted biopsies be performed per target, as is the clinical standard currently, to minimize patient procedure-related morbidity.

**Competing interests:** Dr. Cooper has been an advisor for and is a minority shareholder in Vena Medical Inc. Dr. Cagiannos has participated in advisory board meetings for AbbVie and Ferring; and has received speaker honoraria from AbbVie, Acerus, and Ferring. Dr. Lavallée has participated in advisory board meetings for Ferring and Sanofi, and received a grant from Sanofi. Dr. Morash has participated in advisory board meetings for AbbVie, Astellas, Ferring, Janssen, and Sanofi, and participated in the CRONOS II clinical trial supported by AbbVie. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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