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1 **LEARNING CURVE OF FUSION MRI-TARGETED PROSTATE BIOPSY AND 3D-**
2 **TRUS SEGMENTATION**

3
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24
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28 Figures (3)

29 **Conflict of Interest:** Pierre Mozer and Jocelyne Troccaz are co-inventors in the
30 patents for the targeted biopsy device and have been involved in the license of the
31 Koelis UroStation system. All other authors have nothing to disclose

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- 1 *Biopsy**; *Magnetic Resonance Imaging**; *Imaging, Three-Dimensional** / *methods*;
- 2 *Learning Curve* ; *Ultrasonography / methods**; *Prostate** / *diagnostic imaging* ; *Biopsy*
- 3 / *methods**
- 4

1 **ABSTRACT**

2

3 **Purpose:** To report the learning curve of fusion MRI-targeted biopsy of multiple

4 operators and determine the number of cases needed to achieve proficiency

5 **Materials and Methods:** All adult males who underwent fusion MRI targeted-biopsy

6 biopsy between February 2012 and July 2021 for clinically suspected prostate cancer

7 in a single center were included. Fusion transrectal MRI-targeted biopsy was

8 performed under local anesthesia using the Koelis platform. Learning curves for the

9 segmentation of transrectal ultrasound (TRUS) images and the overall MRI targeted-

10 biopsy procedure were estimated with Locally Weighted Scatterplot Smoothing by

11 computing each operator's timestamps for consecutive procedures. Non-risk-

12 adjusted cumulative sum methods (CUSUM) were used to create learning curves for

13 clinically significant prostate cancer (i.e. ISUP \geq 2) detection.

14 **Results:** Overall, 1721 patients underwent MRI-targeted biopsy in our center during

15 the study period. The median time for TRUS segmentation and MRI targeted-biopsy

16 procedure was 4.5 min (IQR:3.5,6.0) and 13.2 min (IQR:10.6,16.9), respectively.

17 Among the 14 operators with more than 50 cases, a plateau was reached after 40

18 cases for the TRUS segmentation time and 50 cases for the overall MRI targeted-

19 biopsy procedure time. CUSUM showed that the learning curve for clinically significant

20 prostate cancer detection required 25 to 45 procedures to achieve clinical proficiency.

21 Pain scores ranged between 0-1 for 84% of patients, and a plateau phase was reached

22 after 20 to 100 cases.

23 **Conclusions:** A minimum of 50 cases of MRI-targeted biopsy are necessary to

24 achieve clinical and technical proficiency and reach reproducibility in terms of timing,

25 clinically significant prostate cancer detection, and pain.

26

1 **Introduction**

2 Multiparametric magnetic resonance imaging (MRI) has become the reference
3 diagnostic tool for prostate cancer (PCa) diagnosis[1, 2]. Its high sensitivity and
4 specificity in identifying target lesions have made it a cornerstone of PCa diagnosis by
5 allowing biopsies to be targeted towards these lesions[3]. This strategy has improved
6 the detection rate of clinically significant PCa (csPCa; i.e., \geq ISUP 2) while decreasing
7 the detection rate of non-significant PCa, compared to 12-standard sextant biopsies[4,
8 5]. Among the MRI-targeted biopsy techniques, fusion biopsy, which combines MRI
9 images with real-time ultrasound, has gained popularity due to its accuracy and
10 reproducibility[6, 7]. However, despite the improved accuracy in reaching small targets
11 and the ability to perform precise planning and tracking of each biopsy core compared
12 to cognitive biopsy[8], there is a learning curve associated with the technique of fusion
13 targeted biopsy, which may impact the accuracy and proficiency of the procedure.
14 The available literature on the learning curve of fusion biopsy is limited, primarily
15 consisting of a small number of studies[9], single-operator analyses[10, 11], or simple
16 time-period comparisons[12]. These studies lack sufficient data regarding the overall
17 procedure duration and qualitative evaluation of the cancer detection rate during the
18 learning process. Additionally, there is a lack of consensus regarding the number of
19 cases required to attain proficiency. Finally, there is a scarcity of accessible data
20 specifically addressing the learning curve associated with segmentation.
21 Therefore, this study aimed to evaluate the learning curve of fusion MRI-targeted
22 biopsy in a high-volume center with multiples operator and determine the number of
23 cases needed to achieve proficiency through the analysis of cancer detection, time for
24 the overall biopsy procedure and segmentation, and patient-reported outcome for the
25 evaluation of pain.

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Materials and Methods

Study design

In this study, we prospectively collected the data from all adult males (≥ 18 years old) who consecutively underwent fusion MRI-targeted prostate biopsy between February 2012 and July 2021 for clinically suspected prostate cancer in a single center. Patients with elevated prostate-specific antigen (PSA) levels (i.e., ≥ 4 ng/mL) or abnormal digital rectal examination (DRE) results were recommended to undergo prostate MRI. Those with a lesion exhibiting a Prostate Imaging Reporting and Data System (PIRADS) or Likert score of 3 or higher were eligible for targeted biopsy. Patients who underwent systematic biopsies only or those who did not undergo MRI before the biopsy were excluded from the study. Approval for this investigation was obtained from the local Institutional Review Board and Ethics Committee (Comité de Protection des Personnes, decision 30062004).

MRI and targeted biopsy protocol

Patients underwent multiparametric MRI as described previously[13, 14]. Prostate biopsy was performed using the Koelis platform for the computer-assisted fusion of labeled T2-weighted MRI images over real-time prostate ultrasound scans, as reported previously. The MRI and the ultrasound images were segmented using a probabilistic atlas and a spatially constrained deformable model [15]. Once the 3D contours were defined on the MRI and the ultrasound images by the biopsy operator, the fusion of the acquired data was done according to the elastic image fusion model[16]. Transrectal prostate biopsies were performed by physicians (N=31) with different levels of experience, ranging from no experience to expert. All novice operators were

1 supervised by a trained lead operator who oversaw the early stages of their learning,
2 providing guidance to ensure consistency in the practices and decisions of all
3 operators[14]. This lead operator explained the technique and the device before the
4 first procedure and remained available to assist any novice operator upon request,
5 without being systematically present during the procedure. All biopsy specimens were
6 analyzed by a senior genitourinary pathologist with more than ten years of experience,
7 who graded the biopsy according to the ISUP classification using grades from 1 to 5,
8 reflecting the increasing severity of the disease. Tumor differentiation was determined
9 using the Gleason score, and the highest Gleason score for each biopsy was recoded
10 to ISUP grade[17, 18]. All results are presented according to START (Standards of
11 Reporting for MRI-TB Studies) recommendations[19].

12

13 *Data collection*

14 Clinical data were prospectively collected and securely entered into an anonymized
15 database by a data manager who was not involved in patient care. At the time of
16 biopsy, anonymization was achieved by assigning a computer-generated random
17 number to each patient. Timestamps for each step of the biopsy procedure were
18 automatically stored prospectively in the fusion biopsy system without human
19 intervention.

20 Pain levels reported by the patient after the procedure were measured using a 0 to 10
21 visual analog scale and recorded by the nurse on a dedicated form in the medical chart.

22 This database received approval from the « Commission Nationale de l'Informatique
23 et des Libertés » (CNIL).

24

25

1 *Statistical analysis*

2 Descriptive statistics were obtained, reporting median and interquartile range (IQR) for
3 continuous variables and frequencies and proportions for categorical variables, as
4 appropriate. Continuous variables were analyzed with the Wilcoxon test. Differences
5 between categorical variables were assessed using the Chi 2 and Fisher exact tests
6 when appropriate.

7 Learning curves were estimated for all operators with more than 50 cases of
8 experience through sequential analysis, starting with the first fusion MRI-targeted
9 biopsy case. The TRUS segmentation time was calculated as the time delay between
10 the TRUS acquisition's time stamp and the first biopsy's time stamp.

11 The time for the overall combined biopsy procedure (systematic 12 cores biopsies +
12 2-4 targeted cores) was calculated as the time delay between the TRUS acquisition's
13 time stamp and the last biopsy's time stamp. Learning curves for the segmentation of
14 TRUS images (Figure 1) and the overall biopsy procedure (Figure 2) were estimated
15 by computing each operator's time for consecutive procedures. For the overall biopsy
16 procedure, the duration of the combined biopsy (i.e., 12 systematic cores + 2-6
17 targeted cores) was adjusted to the total number of cores. Locally Weighted Scatterplot
18 Smoothing (LOWESS) methods were applied to the segmentation and overall
19 procedure learning curve to help visualize trends in the curve.

20 The statistical method of Cumulative Sum (CUSUM) was used to track the evolution of
21 operators' diagnostic performance over time by recording the detection rates of
22 clinically significant cancer in each consecutive biopsy. The objective was to detect
23 potential variations in the results and identify periods of improvement or deterioration
24 in performance for each operator. To apply CUSUM to the biopsy learning curve, the
25 cumulative sum of the differences between the observed and the expected results were

1 calculated for each procedure. The expected csPCa detection rate was set at 40%,
2 considering the detection rates of our database's most experienced operator, who had
3 an overall prostate cancer (PCa) detection rate of 60%, and a 40% rate for csPCa.
4 This detection rate was similar to the 38% csPCa detection rate reported by Borkowetz
5 et al. for targeted fusion biopsy[20]. Non-risk-adjusted CUSUM methods were used
6 retrospectively to create learning curves for fusion targeted biopsy for csPCa detection
7 (Figure 3). The observed minus expected CUSUM curves (O-E CUSUM) were
8 generated, and LOWESS methods were applied to the O-E CUSUM plots to help
9 visualize trends in the curve. In addition, the cumulative log-likelihood CUSUM curve
10 was generated (supplementary materials, Figure S1) to highlight significant changes
11 in a surgeon's performance in a more sensitive manner than the traditional cumulative
12 sum method. Indeed, the log-likelihood ratio method utilizes the probability of each
13 result to detect significant changes in performance, whereas the cumulative sum
14 method only considers the differences between the observed results and the expected
15 results. Control limits were determined using a simulation method [21] and were based
16 on detecting a 100% increase (odds ratio = 2) or 50% decrease (odds ratio = 0.5) in
17 the odds of experiencing the outcome with a Type-I error rate of 10%.

18 The learning curves for pain were computed using the pain score reported by the
19 patient at the end of the procedure, measured with a visual analogic scale ranging from
20 0 to 10. Statistical analyses were performed using R statistical software v.3.4.0 (R
21 Foundation for Statistical Computing, Vienna, Austria). All univariate tests were two-
22 sided with a significance set at $P < 0.05$.

1 **Results**

2

3 *Study population*

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5 Overall, 1721 patients underwent targeted biopsy in our center during the study period.

6 Among the included patients, 695 (40%) and 357(20%) were diagnosed with csPCa

7 and non-clinically significant prostate cancer (i.e., ISUP 1) on the targeted cores,

8 respectively (Table 1). A total of 31 physicians performed the targeted biopsies, of

9 whom 14 performed at least 50 procedures.

10

11 *Learning curve for TRUS segmentation*

12 The median time for TRUS segmentation was 4.5 min (IQR 3.5,6.0) in the overall

13 cohort. Among the 14 operators with more than 50 cases, a plateau was reached after

14 40 cases for the TRUS segmentation time (Figure 1).

15

16 *Learning curve for combined biopsy*

17 The median time for combined targeted biopsy from TRUS segmentation until the last

18 biopsy was 13.2 min (IQR 10.6, 16.9). Among the 12 operators with more than 50

19 cases, a plateau was reached after 50 cases, after which the time for combined

20 targeted biopsy adjusted on the total number of cores was stable (Figure 2).

21

22 *Learning curve for csPCa detection using CUSUM*

23 Data for the detection of csPCa was available for 947 patients who underwent

24 combined targeted biopsy by eight operators with more than 50 cases of experience.

1 Based on the O-E CUSUM curve for the csPCa detection, a plateau where the CUSUM
2 curve appears to reach a local maximum within 45 procedures for operators A and N,
3 48 for M, and 25 for CGT (Mean = 40). The other operators did not seem to reach this
4 plateau (Figure 3)

5 The log-likelihood CUSUMs for the four surgeons who reached the plateau show that
6 the upper boundary was crossed after approximately 25 cases for operator A, meaning
7 the rate of csPCa reached the specified acceptable level. For the others, the upper
8 boundary was not crossed, but the trend in the curves showed a rise after
9 approximately 40 to 50 cases (supplementary materials, Figure S1).

10

11 *Learning curve for pain*

12 Data about pain during the combined targeted biopsy was available for five operators
13 with more than 50 cases of experience, who performed a total of 666 procedures.

14 Overall, the pain score during targeted biopsy ranged between 0-1 out of 10 for 84%
15 (N=548) of patients. The plateau was reached after 20 cases for two operators (K and
16 F), around 35 cases for B, and around >100 cases for H and D (supplementary
17 materials, Figure S2).

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1 **Discussion**

2

3 Targeted prostate biopsy is now recommended as the first-line diagnostic strategy for
4 patients with MRI-visible lesions. However, most urologists practice cognitive targeted
5 biopsy, and fusion biopsies have not become widely popular, probably because of the
6 greater complexity, which nevertheless allows for superior planning accuracy and
7 quality control with tracking of each core. To the best of our knowledge, no study has
8 evaluated the learning curve of fusion MRI-targeted biopsy with elastic MRI-TRUS
9 fusion and organ-based tracking.

10 A previous study by Calio et al. including 1528 patients who had fusion biopsies with
11 probe-based tracking, was a comparison of biopsy outcomes from three consecutive
12 periods in a single institution[12]. There was no precise analysis of consecutive cases
13 for each operator and, therefore, no attempt to model the relationship between
14 experience and outcome. As stated by Vickers, this approach of arbitrarily dividing the
15 data by date and comparing different periods often leads to completely unwarranted
16 conclusions based on the way the groups were divided[22]. The study by Mager et al.
17 compared the results of an experienced and a novice operator who respectively
18 performed 42 and 84 procedures using a rigid MRI-TRUS fusion and probe-based
19 tracking system[9]. The limited number of patients and operators precluded the
20 generalization of their results and did not allow for the determination of the number of
21 cases needed to achieve proficiency. Furthermore, in a study conducted by Halstuch
22 et al., the efficiency and proficiency measured by timing and cancer detection rates,
23 respectively, were assessed. This study focused on a single operator who performed
24 318 transrectal biopsies on PIRADS 3 targets and demonstrated that proficiency was
25 attained after 110 procedures. However, the findings of this study may not be
26 generalizable due to the single-operator design, the learning curve calculated only from

1 biopsies of PIRADS 3 lesions, and the use of two different rigid-fusion biopsy platforms
2 by the operator.

3

4 Against this backdrop, we computed the learning curves using the main clinically
5 pertinent outcomes for a series of consecutive cases involving 14 operators, all of
6 whom used the same elastic-fusion biopsy platform (Koelis™). We determined that
7 overall, 40 to 50 cases are needed to achieve technical and clinical proficiency for MRI-
8 fusion biopsy using the Koelis system.

9 Specifically, the technical learning phase for the time of TRUS segmentation is
10 completed after 40 cases with a median time required of 4.5 minutes. At the time of
11 writing, the specific learning curve of TRUS segmentation has never been assessed.
12 Thus, our findings are essential to estimate the extent of learning related to the
13 planning phase and to consider the potential benefits of automating the TRUS
14 segmentation through innovations in artificial intelligence algorithms[23, 24]. Indeed,
15 the automation of this phase could potentially result in a 30% reduction in the overall
16 procedure time. In the present study, we did not include the MRI segmentation in the
17 learning curve of the planning. The main reason is that the MRI segmentation was
18 often performed before the biopsy sessions, and the associated time stamps were not
19 relevant in this case. Moreover, as it can be performed beforehand, it has no impact
20 on the time the patient spends with the probe in the rectum or on the occupancy time
21 of the biopsy room, which was estimated at 13.2 minutes in our study.

22 The learning curves for the duration of the overall biopsy procedure adjusted on the
23 total number of cores seem to reach a local maximum after 50 cases, indicating that at
24 that point, the operator has achieved a certain level of technical proficiency. Afterward,
25 the curve stabilizes for all operators, suggesting that technical acquisition remains

1 stable after the initial learning phase. Our findings are similar to those presented by
2 Stabile et al., who examined the learning curve for MRI-TB in a single-operator setting,
3 where either fusion MRI-TB or cognitive MRI-TB was performed[11]. Interestingly, they
4 demonstrated a significant improvement after 60 fusion MRI-TB cases, which aligns
5 with our results. Additionally, in the aforementioned study, the learning curve for
6 cognitive biopsy did not appear to reach a plateau phase within the first 80 cases,
7 which suggests that the use of software-based registration may expedite the learning
8 curve[11]. While the single-operator design of their study prevents definitive
9 conclusions, this hypothesis aligns with the conclusions of the PROFUS trial, which
10 indicate that the use of software-assisted fusion MRI-TB could reduce the learning
11 curve required for visual targeting and enhance the adoption of MRI-TB in the medical
12 community[8].

13 Secondly, we analyzed cancer detection with the CUSUM statistical method seeking
14 to corroborate the findings for technical outcomes (e.g., operative time) and find any
15 tendency that could reflect any improvement in surgical proficiency. The CUSUM
16 analysis of csPCa detection showed that there was a progressive improvement over
17 the first 40 cases, reflected by the positive slope of the CUSUM curve, then a
18 stabilization of performance from around 50 cases, reflecting the achievement of a
19 proficiency level. This result is consistent with the learning curve analysis of
20 segmentation and overall biopsy time, which suggests that the learning phase lasts
21 approximately 40 cases. The csPCa detection rate is an overall quality metric
22 depending on several factors such as the accuracy of the planning, the quality of the
23 registration, the ability to reach the target, but also by the adequate selection of the
24 patient.

1 Last, we evaluated the pain reported by the patient at the end of the biopsy procedure.
2 Patient-reported outcomes are necessary to integrate the patient's perception in the
3 learning curve analysis and to see if there is an improvement from this perspective.
4 Overall, the pain associated with the transrectal biopsy procedure under local
5 anesthesia was minimal for a large majority of patients. It is worth noting that the
6 decrease in overall procedure time during the learning process did not lead to
7 increased pain for the patient. On the contrary, we observed a gradual improvement in
8 patients' pain perception as the operator gained more experience. However, unlike the
9 other evaluated parameters, the number of cases to reach the plateau phase is
10 variable according to the operators and ranges from 20 to 100 cases.

11

12 Our study is not devoid of limitations. First, CUSUM methods were non-risk-adjusted,
13 meaning differences in the case mix were not accounted for in the analysis, which
14 could be responsible for some bias. Second, although we included a large number of
15 operators from the beginning of their experience, the study was conducted in a tertiary
16 care center where MRI-targeted biopsies were pioneered. Therefore, our results might
17 not be entirely transferable in a center without experience with MRI-targeted biopsy.
18 Third, our database did not capture data on post-biopsy complications. Although the
19 connection between operator experience and the likelihood of post-biopsy
20 complications remains unclear, a thorough analysis dedicated to quality control would
21 be interesting to investigate this potential correlation

22

23 **Conclusion**

24 A minimum of 50 cases are necessary to achieve clinical and technical proficiency
25 and reach reproducibility in terms of TRUS segmentation and MRI-TB times, csPCa

1 detection, and pain. However, there is notable variability among operators, which
2 showcases their individual development and evolving expertise as they progress
3 toward technical mastery.

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1 **Figure Legends**

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Figure 1. Learning curves for 3D- TRUS segmentation

3D-TRUS: three-dimensional transrectal ultrasound

Figure 2. Learning curves of operative time adjusted on the biopsy cores.

The duration of the combined MRI-TB procedure was adjusted on the total number of biopsy cores. All patients had a minimum of 12 systematic cores and 2 targeted cores.

MRI-TB: MRI-targeted prostate biopsy

Figure 3. Learning curves for Clinically significant prostate cancer detection using the CUSUM methods

Expected csPCa set at 60% based on expert detection rate in our series and other studies (see material and methods section)

CUSUM: cumulative sum ; CsPCa : Clinically significant prostate cancer (i.e. \geq ISUP 2)

Table 1. Baseline Characteristics of the study population

Characteristics	Overall, N = 1,721	ISUP 0-1, N = 1,026	ISUP ≥ 2 , N = 695	p-value
Age — years	66.0 (61, 72)	65.0 (60, 70)		<0.001
MRI Prostate Volume — cc (IQR)	47.2 (34.5, 65.7)	53.1 (37.8, 71.2)	40.6 (31, 54.2)	<0.001
PSA — ng/ml (IQR)	7.0 (5, 10)	6.0 (5, 9)	8.0 (5, 12)	<0.001
MRI done at the host center (%)				<0.001
No	326 (24)	162 (20)	164 (29)	
Yes	1,033 (76)	641 (80)	392 (71)	
Likert Score — no. (%)				<0.001
2	13 (1.1)	11 (1.7)	2 (0.4)	
3	198 (17)	171 (27)	27 (5.2)	
4	460 (40)	269 (42)	191 (37)	
5	492 (42)	192 (30)	30 (58)	
No. of cores on MRI-targeted biopsy — no. (IQR)	3.0 (2, 4)	3.0 (2, 4)	4.0 (3, 5)	<0.001
Previous biopsy result — no. (%)				<0.001
Positive	151 (8.9)	108 (11)	43 (6.2)	
Negative	262 (15)	168 (17)	94 (14)	
No Previous biopsy	1,289 (76)	732 (73)	557 (80)	
Missing	19	18	1	
Target localisation				0.3
Anterior	427 (27%)	246 (26%)	181 (28%)	
Posterior	1,179 (73%)	716 (74%)	463 (72%)	
Total length of targeted biopsy cores - mm	38 (26, 54)	34 (24, 49)	45 (32, 60)	<0.001
Total length of cancer on targeted biopsy cores - mm	16 (7, 28)	8 (4, 18)	20 (11, 32)	<0.001

PSA: Prostate-specific antigen; IQR: interquartile range; ISUP: Prostate cancer grade according to the International society of urological pathology;

Figure 1

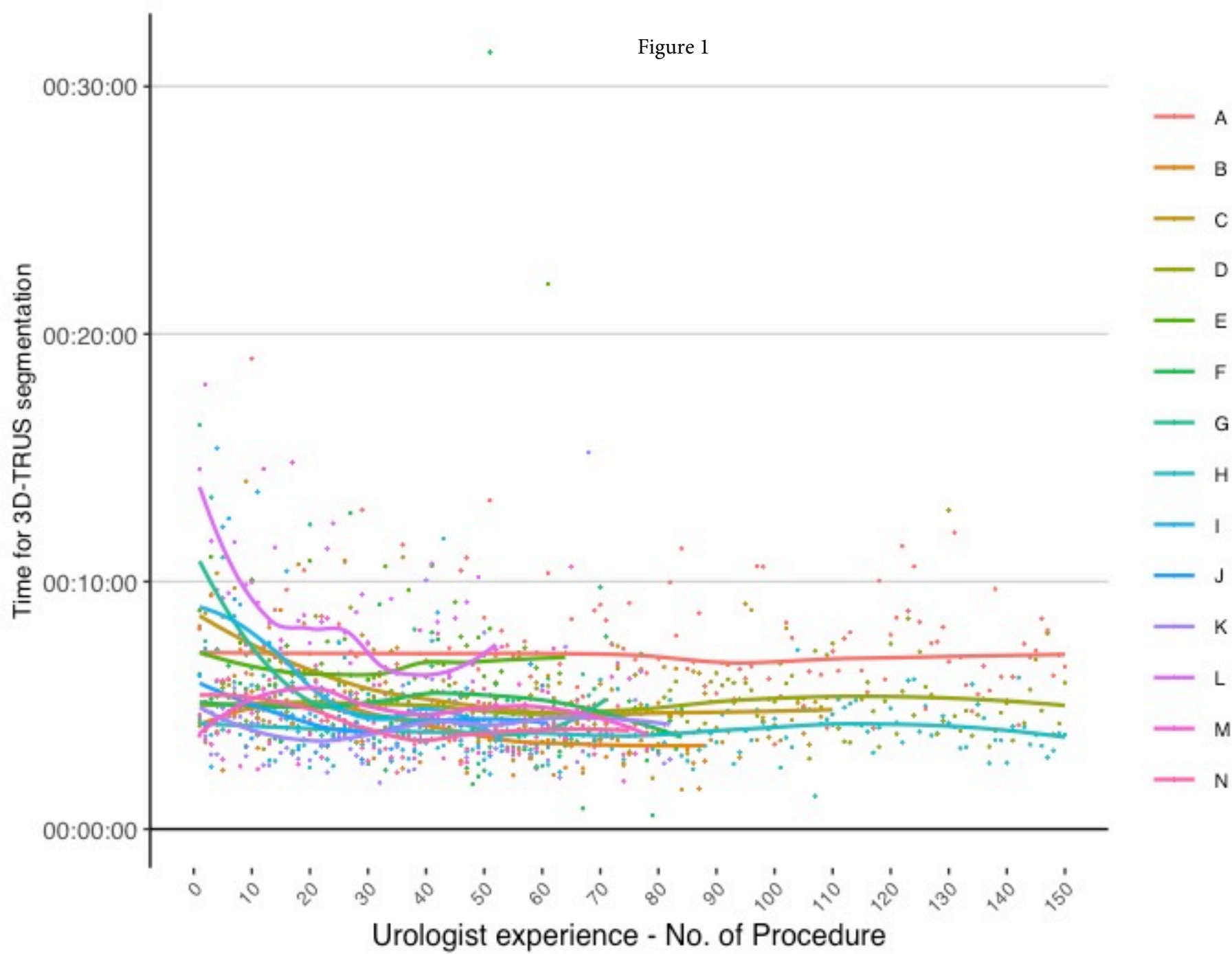
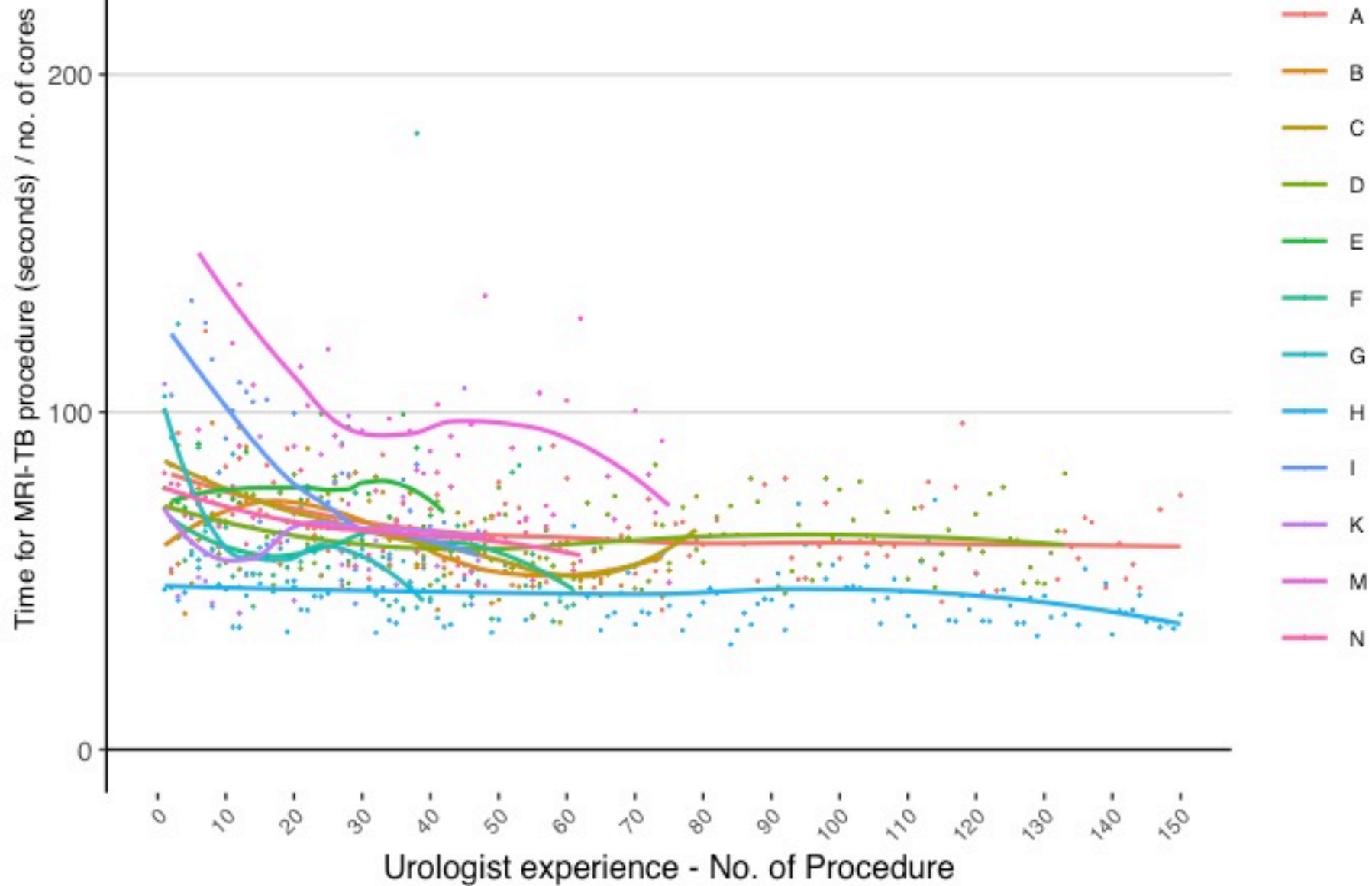


Figure 2



Cumulative Observed - Expected csPCa detection

Figure 3

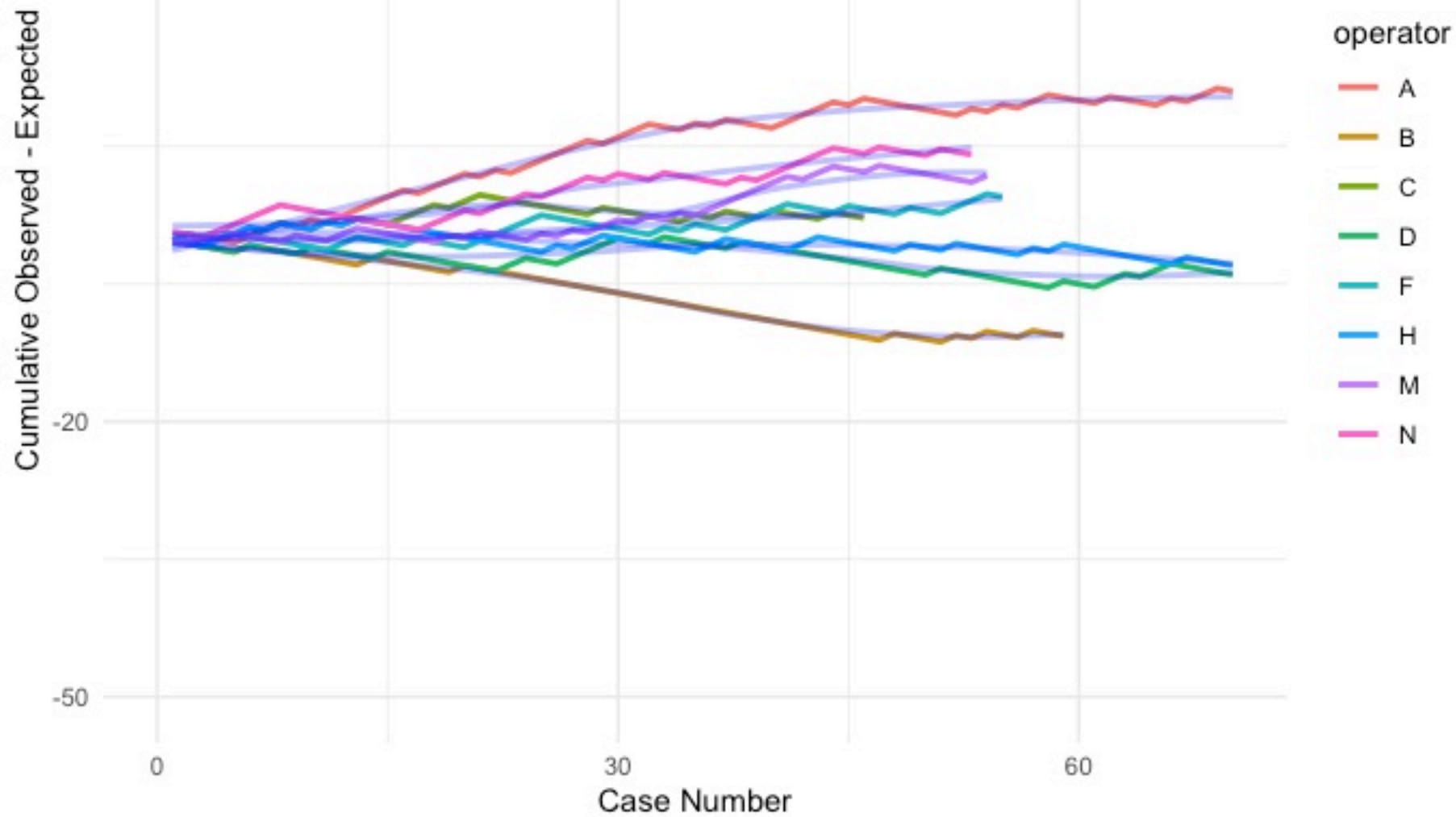
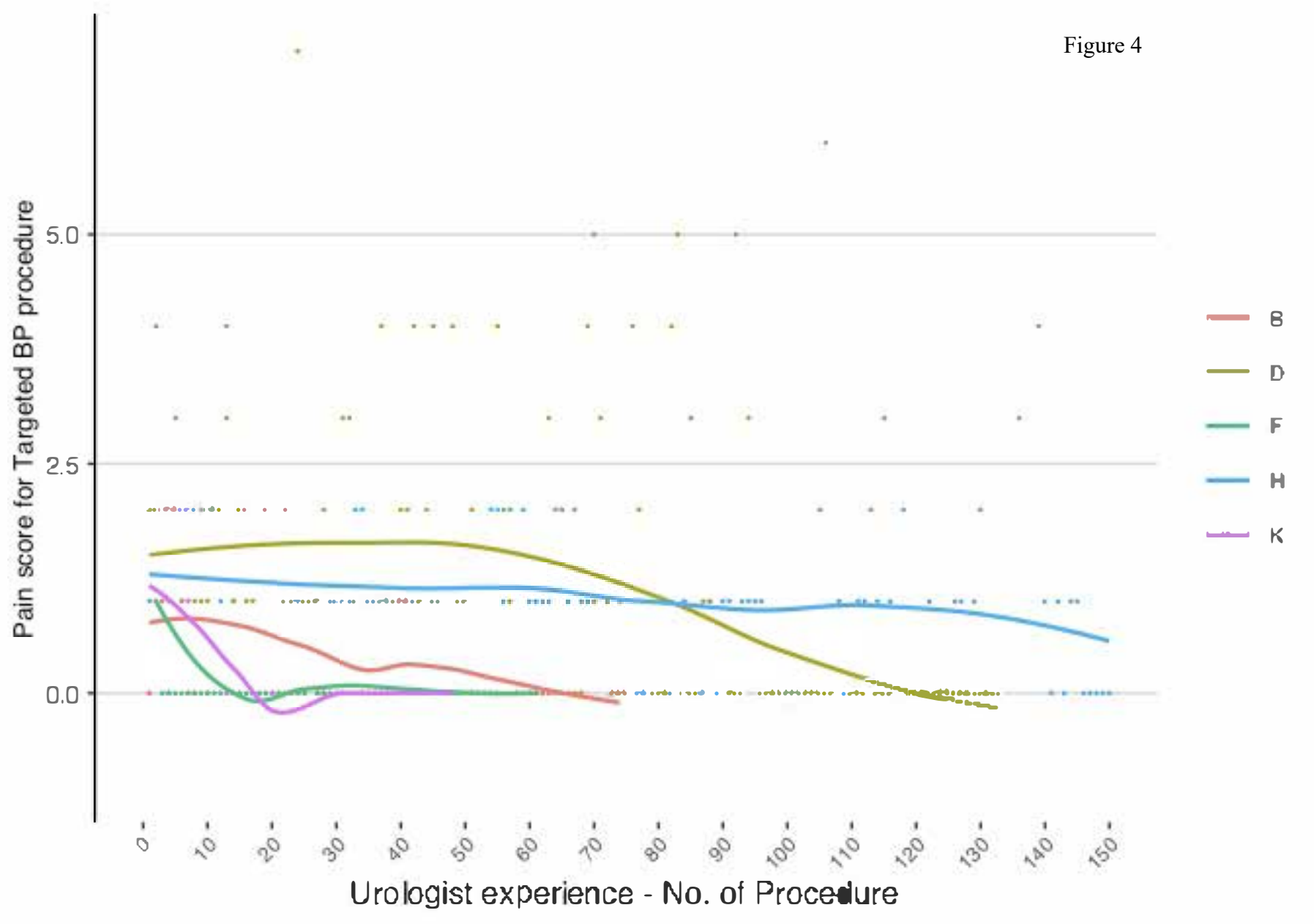


Figure 4



Supplementary materials

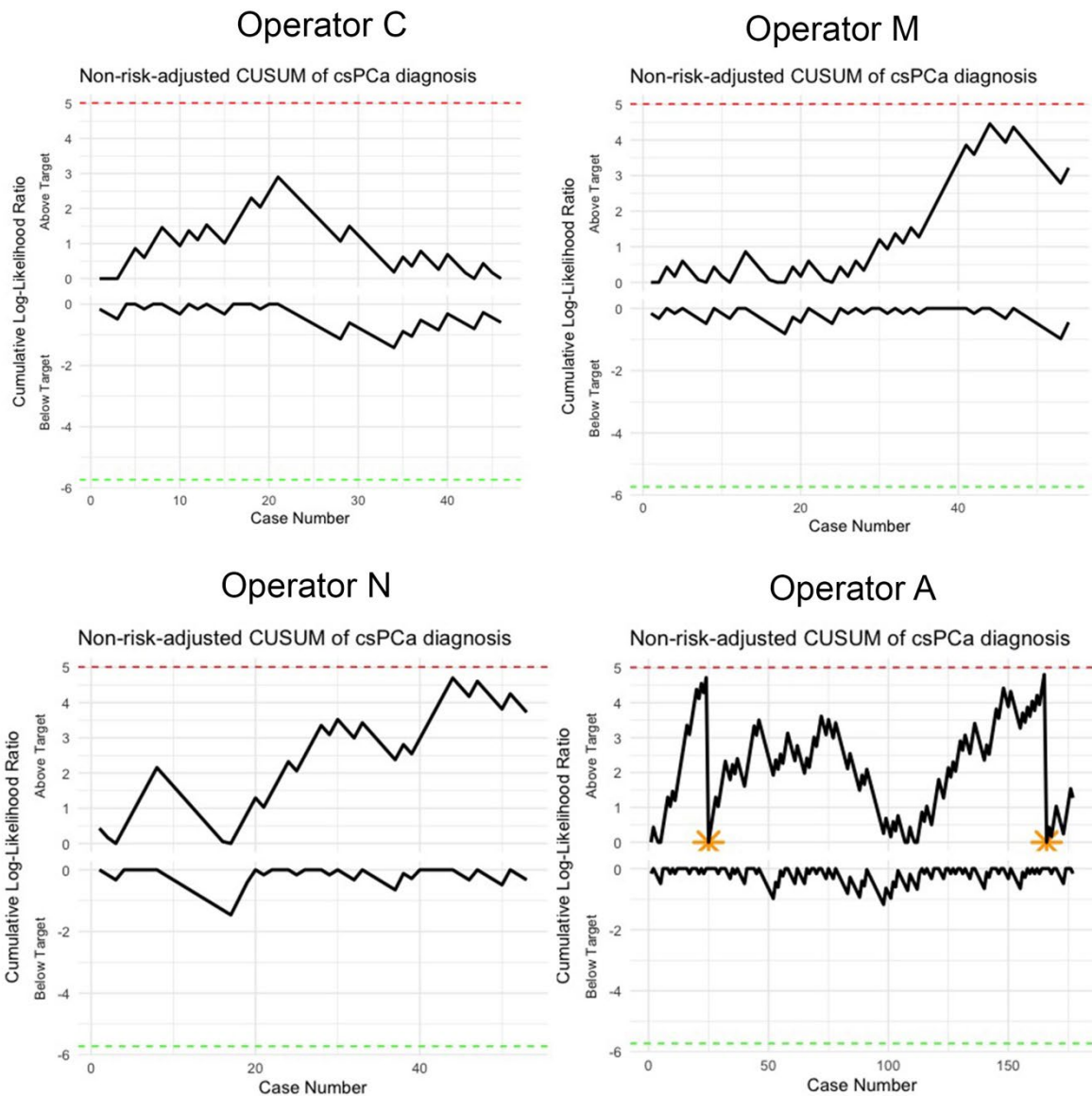


Figure S1 Analysis using the cumulative log-likelihood ratio method for certain operators. This method allows for highlighting significant changes in a surgeon's performance more sensitively than the traditional cumulative sum method. Indeed, the log-likelihood ratio method utilizes the probability of each result to detect significant changes in performance, whereas the cumulative sum method only considers the differences between the observed results and the expected results.

CUSUM: Cumulative sum ; CsPCa : Clinically significant prostate cancer

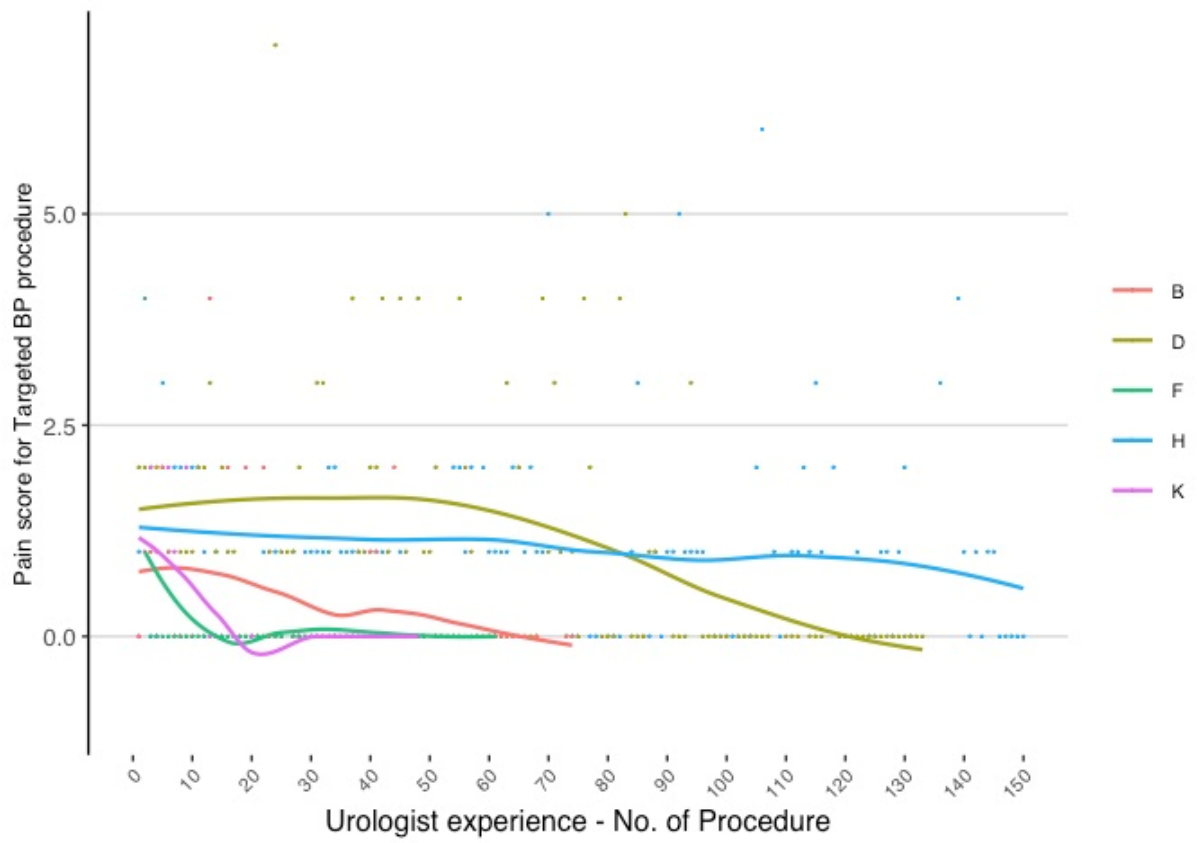


Figure S2. Learning curves for Patient's pain perception

The pain was measured with a visual analogic scale ranging between 0 and 10.