# APPLICATION OF ACTIVE SURVEILLANCE THRESHOLD TO SERIES OF SAMPLES SUBMITTED FOR COMMERCIAL TESTING

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#### INTRODUCTION

- Active surveillance (AS) is an increasingly popular treatment modality for men with localized prostate cancer.
- Recently, we developed a method to select men for AS based on a score that combines cell cycle progression (CCP) with CAPRA (combined clinical CCP risk (CCR) score).
- Here, we apply our validated AS CCR threshold to a series of samples submitted for commercial testing.

### METHODS

# **Patients**

- Samples from 11,665 patients were submitted by their physicians to Myriad Genetic Laboratories for CCP analysis with sufficient tissue for testing.
- Patient clinicopathological data were obtained from the test request form.

#### **Gene Expression Testing**

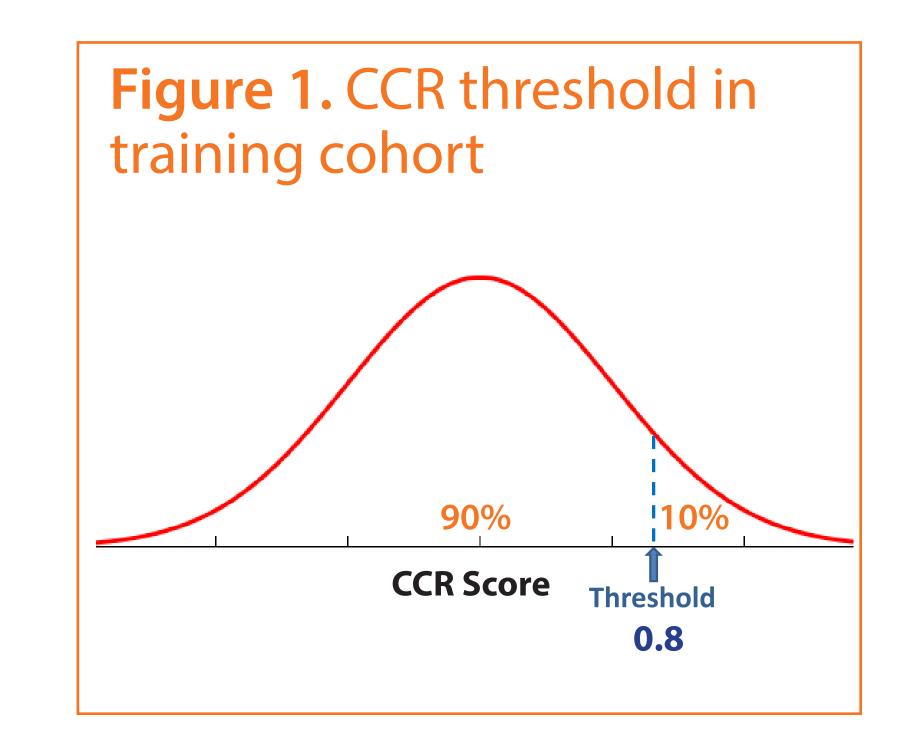
- Formalin-fixed paraffin-embedded surgical tumor samples were analyzed for the expression levels of 31 CCP genes and 15 house-keeping genes by quantitative RT-PCR.
- The CCP Score is an un-weighted average of the cell cycle genes normalized by the average of housekeeping genes.
- Scores ranged from -2.9 to 4.1.
- The CCR score is the proportional hazard model combination of CAPRA and CCP scores
- $(0.57 \times CCP \text{ score}) + (0.39 \times CAPRA \text{ score})$

#### **Statistical Methods**

The clinicopathological data of patients with a CCR score meeting the AS threshold (≤ 0.8) were analyzed focusing on their PSA, % positive cores, Gleason score, stage, AUA risk classification, and CAPRA score.

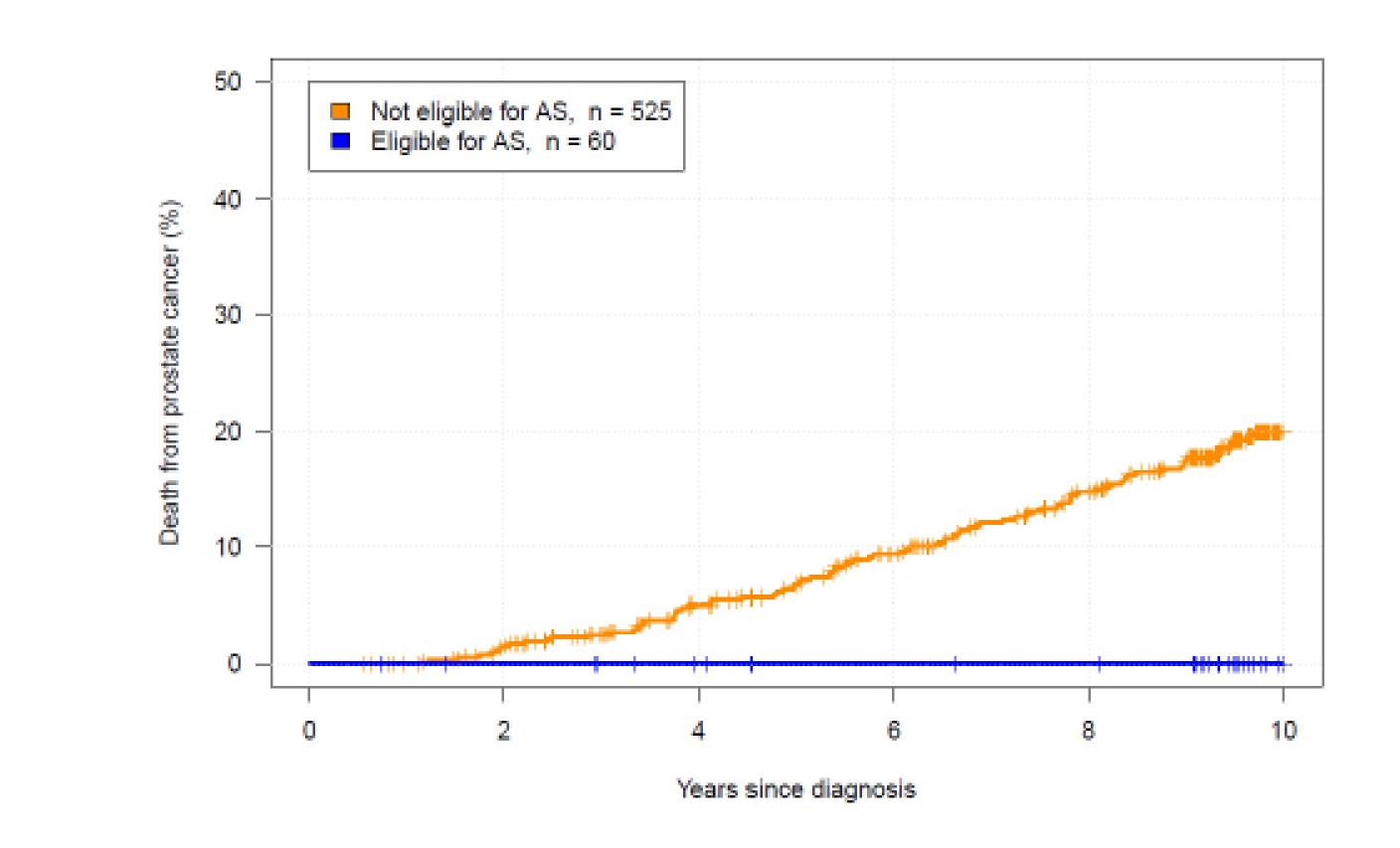
#### CCRTHRESHOLD

- A CCR threshold has been previously developed in a training cohort of men who might typically be considered for AS based on their clinical characteristics alone (N=505).
- The training cohort consisted of men with: Gleason score  $\leq$  3+4, PSA < 10 ng/ml, < 25% cores positive, Clinical stage ≤ T2a.
- A threshold of 0.8 was selected such that 90% of the men in the training cohort had scores below the threshold (Figure 1).
- This threshold was validated in two independent cohorts of conservatively managed men with known outcomes (combined N=765).



- In the validation cohort, the average risk was 2.6% for men below the threshold (low risk) and 21.4% for men above the threshold (high risk) (Figure 2).
- There were no prostate cancer deaths in patients below the threshold (survival data were censored at 10 years).

Figure 2. Disease specific risk for low and high risk groups in the combined validation cohort



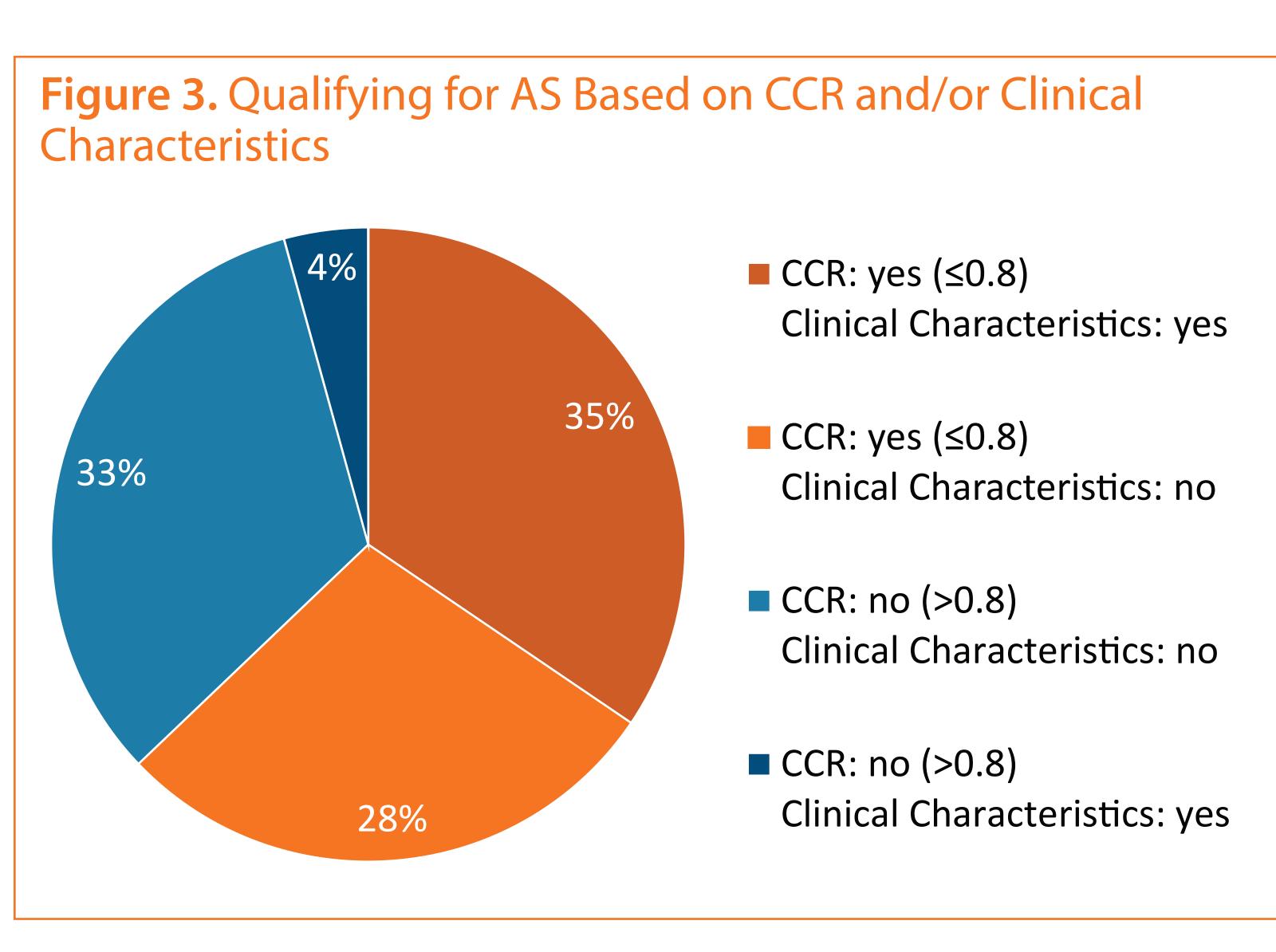
## **Table 1.** Clinical Characteristics of Men with a CCR ≤ 0.8

All Patients Qualifies for AS Does not Qualify

Diagnosis (years)         mean ± sd min, max         64.6 ± 7.9         64.4 ± 7.7         64.8 ± 8.1           PSA (ng/ml)         0 − 4         1,715 (23.4%)         1,036 (25.8%)         679 (20.5%)           4.01 − 10         5,318 (72.6%)         2,983 (74.2%)         2,335 (70.6%)           > 10         292 (4.0%)         0         292 (8.8%)           N         7,325         4,019         3,306           mean ± sd         22.4 ± 15.4         12.6 ± 4.6         34.3 ± 15.7           min, max         0, 100         0, 24.1         2.1, 100           Gleason 5000         4         1 (<0.1%)         1 (<0.1%)         0           5 44 (0.2%)         12 (0.3%)         2 (0.1%)         0         2,357 (71.3%)         3,290 (81.9%)         2,357 (71.3%)         3,44=7         1,620 (22.1%)         716 (17.8%)         904 (27.3%)         904 (27.3%)         443=7         30 (0.4%)         0         30 (0.9%)         5+2=7         0         0         0         11 (0.3%)         9         2 (<0.1%)         0         2 (0.1%)         0         2 (0.1%)         0         2 (0.1%)         0         2 (0.1%)         0         2 (0.1%)         0         2 (0.1%)         0         2 (0.1%)         0         2 (0.1%) <th></th> <th>Variable</th> <th>with CCR Score ≤ 0.8 (N=7,325)</th> <th>using Clinical Characteristics (N=4,019)</th> <th>for AS using Clinical Characteristics (N=3,306)</th>		Variable	with CCR Score ≤ 0.8 (N=7,325)	using Clinical Characteristics (N=4,019)	for AS using Clinical Characteristics (N=3,306)
Min, max   27,93   39,91   27,93   39,91   27,93   39,91   27,93   39,91   27,93   39,91   4,01 – 10   5,318 (72.6%)   2,983 (74.2%)   2,335 (70.6%)   > 10   292 (4.0%)   0   292 (8.8%)   M   7,325   4,019   3,306   Mean ± sd   22.4 ± 15.4   12.6 ± 4.6   34.3 ± 15.7   Min, max   0,100   0,24.1   2.1,100   Gleason   4   1 (<0.1%)   1 (<0.1%)   0   0   0   0   0   0   0   0   0	Age at Diagnosis (years)	N	7,325	4,019	3,306
PSA 0 - 4 1,715 (23.4%) 1,036 (25.8%) 679 (20.5%) (19g/ml) 4.01 - 10 5,318 (72.6%) 2,983 (74.2%) 2,335 (70.6%) > 10 292 (4.0%) 0 292 (8.8%) N 7,325 4,019 3,306 mean ± sd 22.4 ± 15.4 12.6 ± 4.6 34.3 ± 15.7 min, max 0,100 0,24.1 2.1,100 Gleason 5 14 (0.2%) 12 (0.3%) 2 (0.1%) 6 5,647 (77.1%) 3,290 (81.9%) 2,357 (71.3%) 3+4=7 1,620 (22.1%) 716 (17.8%) 904 (27.3%) 4+3=7 30 (0.4%) 0 30 (0.9%) 5+2=7 0 0 0 0 4 11 (0.3%) 9 2 (<0.1%) 0 0 0 11 (0.3%) 9 2 (<0.1%) 10 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		mean ± sd	64.6 ± 7.9	$64.4 \pm 7.7$	64.8 ± 8.1
A.01 - 10   5,318 (72.6%)   2,983 (74.2%)   2,335 (70.6%)     > 10   292 (4.0%)   0   292 (8.8%)     N   7,325   4,019   3,306     mean ± sd   22.4 ± 15.4   12.6 ± 4.6   34.3 ± 15.7     min, max   0,100   0,24.1   2.1,100     Gleason   5   14 (0.2%)   12 (0.3%)   2 (0.1%)     6   5,647 (77.1%)   3,290 (81.9%)   2,357 (71.3%)     3+4=7   1,620 (22.1%)   716 (17.8%)   904 (27.3%)     4+3=7   30 (0.4%)   0   30 (0.9%)     5+2=7   0   0   0     8   11 (0.2%)   0   11 (0.3%)     9   2 (<0.1%)   0   2 (0.1%)     10   0   0   0     11a   216 (2.9%)   169 (4.2%)   47 (1.4%)     5tage   71b   60 (0.8%)   3,354 (83.5%)   2,542 (76.9%)     T2a   796 (10.9%)   459 (11.4%)   337 (10.2%)     T2b   222 (3.0%)   0   222 (6.7%)     T2c   133 (1.8%)   0   133 (4.0%)     T3a   2 (<0.1%)   0   0     T3a   2 (<0.1%)   0   0     T3a   2 (<0.1%)   0   0     T3b   0   0   0     AUA Risk   Classification   High Risk   1,984 (27.1%)   716 (17.8%)   1,268 (38.4%)     High Risk   158 (2.2%)   0   158 (4.8%)     CAPRA   Low (0-2)   6,244 (85.2%)   3,856 (95.9%)   2,388 (72.2%)     Intermediate (3-5)   1,081 (14.8%)   163 (4.1%)   918 (27.8%)		min, max	27, 93	39, 91	27, 93
N	PSA (ng/ml)	0 – 4	1,715 (23.4%)	1,036 (25.8%)	679 (20.5%)
Positive Cores (%)  Positive Cores (%)  mean ± sd  mean ± sd  min, max  0, 100  0, 24.1  1 (<0.1%)  1 (<0.1%)  1 (<0.1%)  6 (5,647 (77.1%)  3,290 (81.9%)  3+4=7  1,620 (22.1%)  4+3=7  30 (0.4%)  5+2=7  0  0  0  11 (0.3%)  9  2 (<0.1%)  6  11 (0.2%)  0  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  0  0  0  0  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  0  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  0  0  11 (0.3%)  9  2 (<0.1%)  10  0  0  0  0  0  0  0  Clinical  T1a  216 (2.9%)  169 (4.2%)  47 (1.4%)  5tage  T1b  60 (0.8%)  37 (0.9%)  23 (0.7%)  T1c  5,896 (80.5%)  3,354 (83.5%)  2,542 (76.9%)  T2a  796 (10.9%)  459 (11.4%)  337 (10.2%)  T2b  222 (3.0%)  0  222 (6.7%)  T2c  133 (1.8%)  0  133 (4.0%)  T3a  2 (<0.1%)  0  0  2 (0.1%)  T3b  0  0  0  0  AUA Risk  Low Risk  5,183 (70.8%)  3,303 (82.2%)  1,880 (56.9%)  Intermediate Risk  1,984 (27.1%)  716 (17.8%)  1,268 (38.4%)  High Risk  158 (2.2%)  0  158 (4.8%)  2,388 (72.2%)  Intermediate (3–5)  1,081 (14.8%)  163 (4.1%)  918 (27.8%)		4.01 – 10	5,318 (72.6%)	2,983 (74.2%)	2,335 (70.6%)
Cores (%) mean ± sd		> 10	292 (4.0%)	0	292 (8.8%)
min, max	Positive Cores (%)	N	7,325	4,019	3,306
Gleason 5		mean ± sd	22.4 ± 15.4	12.6 ± 4.6	34.3 ± 15.7
Score         5         14 (0.2%)         12 (0.3%)         2 (0.1%)           6         5,647 (77.1%)         3,290 (81.9%)         2,357 (71.3%)           3+4=7         1,620 (22.1%)         716 (17.8%)         904 (27.3%)           4+3=7         30 (0.4%)         0         30 (0.9%)           5+2=7         0         0         0           8         11 (0.2%)         0         11 (0.3%)           9         2 (<0.1%)		min, max	0, 100	0, 24.1	2.1, 100
6 5,647 (77.1%) 3,290 (81.9%) 2,357 (71.3%) 3+4=7 1,620 (22.1%) 716 (17.8%) 904 (27.3%) 4+3=7 30 (0.4%) 0 30 (0.9%) 5+2=7 0 0 0 8 11 (0.2%) 0 11 (0.3%) 9 2 (<0.1%) 0 2 (0.1%) 10 0 0 0 Clinical T1a 216 (2.9%) 169 (4.2%) 47 (1.4%) T1b 60 (0.8%) 37 (0.9%) 23 (0.7%) T1c 5,896 (80.5%) 3,354 (83.5%) 2,542 (76.9%) T2a 796 (10.9%) 459 (11.4%) 337 (10.2%) T2b 222 (3.0%) 0 222 (6.7%) T2c 133 (1.8%) 0 133 (4.0%) T3a 2 (<0.1%) 0 2 (0.1%) T3b 0 0 0 AUA Risk Classification High Risk 158 (2.2%) 0 158 (4.8%) CAPRA Score Intermediate (3–5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)	Gleason Score	4	1 (<0.1%)	1 (<0.1%)	0
3+4=7		5	14 (0.2%)	12 (0.3%)	2 (0.1%)
4+3=7       30 (0.4%)       0       30 (0.9%)         5+2=7       0       0       0         8       11 (0.2%)       0       11 (0.3%)         9       2 (<0.1%)		6	5,647 (77.1%)	3,290 (81.9%)	2,357 (71.3%)
S+2=7		3+4=7	1,620 (22.1%)	716 (17.8%)	904 (27.3%)
8		4+3=7	30 (0.4%)	0	30 (0.9%)
9 2 (<0.1%) 0 2 (0.1%) 10 0 0 0 Clinical T1a 216 (2.9%) 169 (4.2%) 47 (1.4%) T1b 60 (0.8%) 37 (0.9%) 23 (0.7%) T1c 5,896 (80.5%) 3,354 (83.5%) 2,542 (76.9%) T2a 796 (10.9%) 459 (11.4%) 337 (10.2%) T2b 222 (3.0%) 0 222 (6.7%) T2c 133 (1.8%) 0 133 (4.0%) T3a 2 (<0.1%) 0 2 (0.1%) T3b 0 0 0 AUA Risk Classification High Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%) High Risk 158 (2.2%) 0 158 (4.8%) CAPRA COMPARA Low (0-2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%) Intermediate (3-5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		5+2=7	0	0	0
T1a 216 (2.9%) 169 (4.2%) 47 (1.4%)  T1b 60 (0.8%) 37 (0.9%) 23 (0.7%)  T1c 5,896 (80.5%) 3,354 (83.5%) 2,542 (76.9%)  T2a 796 (10.9%) 459 (11.4%) 337 (10.2%)  T2b 222 (3.0%) 0 222 (6.7%)  T2c 133 (1.8%) 0 133 (4.0%)  T3a 2 (<0.1%) 0 2 (0.1%)  T3b 0 0 0  AUA Risk Classification Intermediate Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%)  High Risk 158 (2.2%) 0 158 (4.8%)  CAPRA Correllation Intermediate (3–5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		8	11 (0.2%)	0	11 (0.3%)
T1a 216 (2.9%) 169 (4.2%) 47 (1.4%) T1b 60 (0.8%) 37 (0.9%) 23 (0.7%) T1c 5,896 (80.5%) 3,354 (83.5%) 2,542 (76.9%) T2a 796 (10.9%) 459 (11.4%) 337 (10.2%) T2b 222 (3.0%) 0 222 (6.7%) T2c 133 (1.8%) 0 133 (4.0%) T3a 2 (<0.1%) 0 2 (0.1%) T3b 0 0 0  AUA Risk Classification Intermediate Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%) High Risk 158 (2.2%) 0 158 (4.8%) CAPRA Low (0-2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%) Intermediate (3-5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		9	2 (<0.1%)	0	2 (0.1%)
T1b 60 (0.8%) 37 (0.9%) 23 (0.7%)  T1c 5,896 (80.5%) 3,354 (83.5%) 2,542 (76.9%)  T2a 796 (10.9%) 459 (11.4%) 337 (10.2%)  T2b 222 (3.0%) 0 222 (6.7%)  T2c 133 (1.8%) 0 133 (4.0%)  T3a 2 (<0.1%) 0 2 (0.1%)  T3b 0 0 0  AUA Risk Classification Intermediate Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%)  High Risk 158 (2.2%) 0 158 (4.8%)  CAPRA Low (0-2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%)  Intermediate (3-5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		10	0	0	0
T1c 5,896 (80.5%) 3,354 (83.5%) 2,542 (76.9%) T2a 796 (10.9%) 459 (11.4%) 337 (10.2%) T2b 222 (3.0%) 0 222 (6.7%) T2c 133 (1.8%) 0 133 (4.0%) T3a 2 (<0.1%) 0 2 (0.1%) T3b 0 0 0  AUA Risk Classification Intermediate Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%) High Risk 158 (2.2%) 0 158 (4.8%) CAPRA CAPRA Low (0-2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%) Intermediate (3-5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)	Clinical Stage	T1a	216 (2.9%)	169 (4.2%)	47 (1.4%)
T2a 796 (10.9%) 459 (11.4%) 337 (10.2%) T2b 222 (3.0%) 0 222 (6.7%) T2c 133 (1.8%) 0 133 (4.0%) T3a 2 (<0.1%) 0 2 (0.1%) T3b 0 0 0  AUA Risk Classification		T1b	60 (0.8%)	37 (0.9%)	23 (0.7%)
T2b 222 (3.0%) 0 222 (6.7%)  T2c 133 (1.8%) 0 133 (4.0%)  T3a 2 (<0.1%) 0 2 (0.1%)  T3b 0 0 0  AUA Risk Classification		T1c	5,896 (80.5%)	3,354 (83.5%)	2,542 (76.9%)
T2c 133 (1.8%) 0 133 (4.0%) T3a 2 (<0.1%) 0 2 (0.1%) T3b 0 0 0  AUA Risk Classification High Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%) High Risk 158 (2.2%) 0 158 (4.8%)  CAPRA Low (0-2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%) Intermediate (3-5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		T2a	796 (10.9%)	459 (11.4%)	337 (10.2%)
T3a 2 (<0.1%) 0 2 (0.1%)  T3b 0 0 0  AUA Risk Classification		T2b	222 (3.0%)	0	222 (6.7%)
T3b 0 0 0  AUA Risk Classification   Intermediate Risk 1,984 (27.1%) 716 (17.8%) 1,268 (38.4%) 158 (2.2%) 0 158 (4.8%)  CAPRA Low (0-2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%)   Intermediate (3-5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		T2c	133 (1.8%)	0	133 (4.0%)
AUA Risk Classification   Low Risk		T3a	2 (<0.1%)	0	2 (0.1%)
Classification         Intermediate Risk       1,984 (27.1%)       716 (17.8%)       1,268 (38.4%)         High Risk       158 (2.2%)       0       158 (4.8%)         CAPRA Score       Low (0-2)       6,244 (85.2%)       3,856 (95.9%)       2,388 (72.2%)         Intermediate (3-5)       1,081 (14.8%)       163 (4.1%)       918 (27.8%)		T3b	0	0	0
High Risk 158 (2.2%) 0 158 (4.8%)  CAPRA Low (0–2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%)  Intermediate (3–5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)	AUA Risk Classifica- tion	Low Risk	5,183 (70.8%)	3,303 (82.2%)	1,880 (56.9%)
High Risk 158 (2.2%) 0 158 (4.8%)  CAPRA Low (0–2) 6,244 (85.2%) 3,856 (95.9%) 2,388 (72.2%)  Score Intermediate (3–5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		Intermediate Risk	1,984 (27.1%)	716 (17.8%)	1,268 (38.4%)
Score Intermediate (3–5) 1,081 (14.8%) 163 (4.1%) 918 (27.8%)		High Risk	158 (2.2%)	0	158 (4.8%)
111tC111tCdiate (3 3) 1,001 (14.070) 103 (4.170) 210 (27.070)	CAPRA Score	Low (0-2)	6,244 (85.2%)	3,856 (95.9%)	2,388 (72.2%)
High (≥6) 0 0		Intermediate (3–5)	1,081 (14.8%)	163 (4.1%)	918 (27.8%)
		High (≥6)	0	0	0

#### RESULTS

- Of the 11,665 patients included in the analysis, 7,325 (62.8%) qualified for AS based on their CCR score.
- A summary of the patients' clinicopathological characteristics is shown in Table 1.
- A substantial number of these patients, 3,306 (45.1%), would not have qualified for AS based on their clinical characteristics alone (Figure 3).



# CONCLUSIONS

- A CCR threshold of 0.8 has been previously validated in a large cohort with known outcomes, with no deaths in low risk men.
- This analysis showed that 62.8% of commercially tested patients qualified for AS, nearly half of whom would not have qualified for AS based on their clinicopathological characteristics alone.
- For patients considering deferred treatment, the CCR score provides significant prognostic information at disease diagnosis.

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