PROSTATE CANCER DETECTION AFTER NEGATIVE BIOPSY: MRI, BIOMARKER OR SYSTEMATIC BIOPSY

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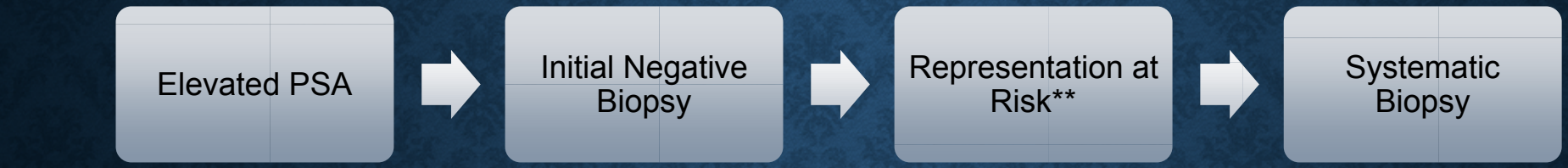
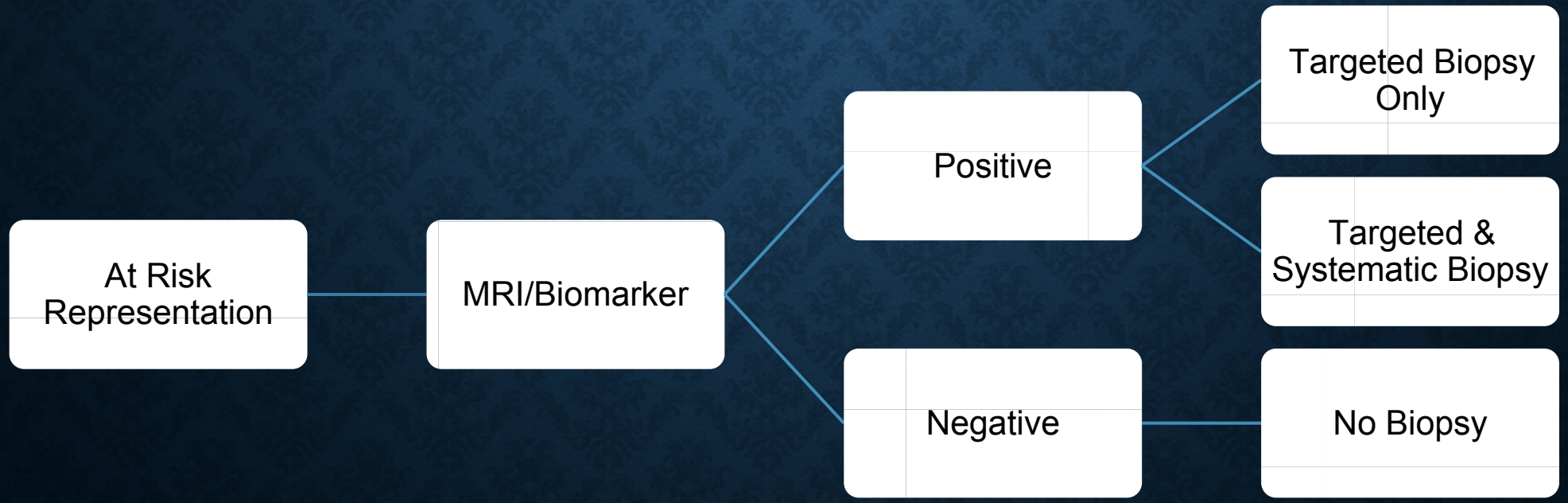
BACKGROUND INFORMATION

- Recent evidence supports MRI and biomarker testing to risk stratify individuals prior to repeat biopsy
- Despite the potential benefits of these minimally invasive strategies, these strategies are:
  - Expensive
  - Not universally available
  - Prone to wide variability in performance at different centres, learning curves

BACKGROUND INFORMATION





RESEARCH QUESTION

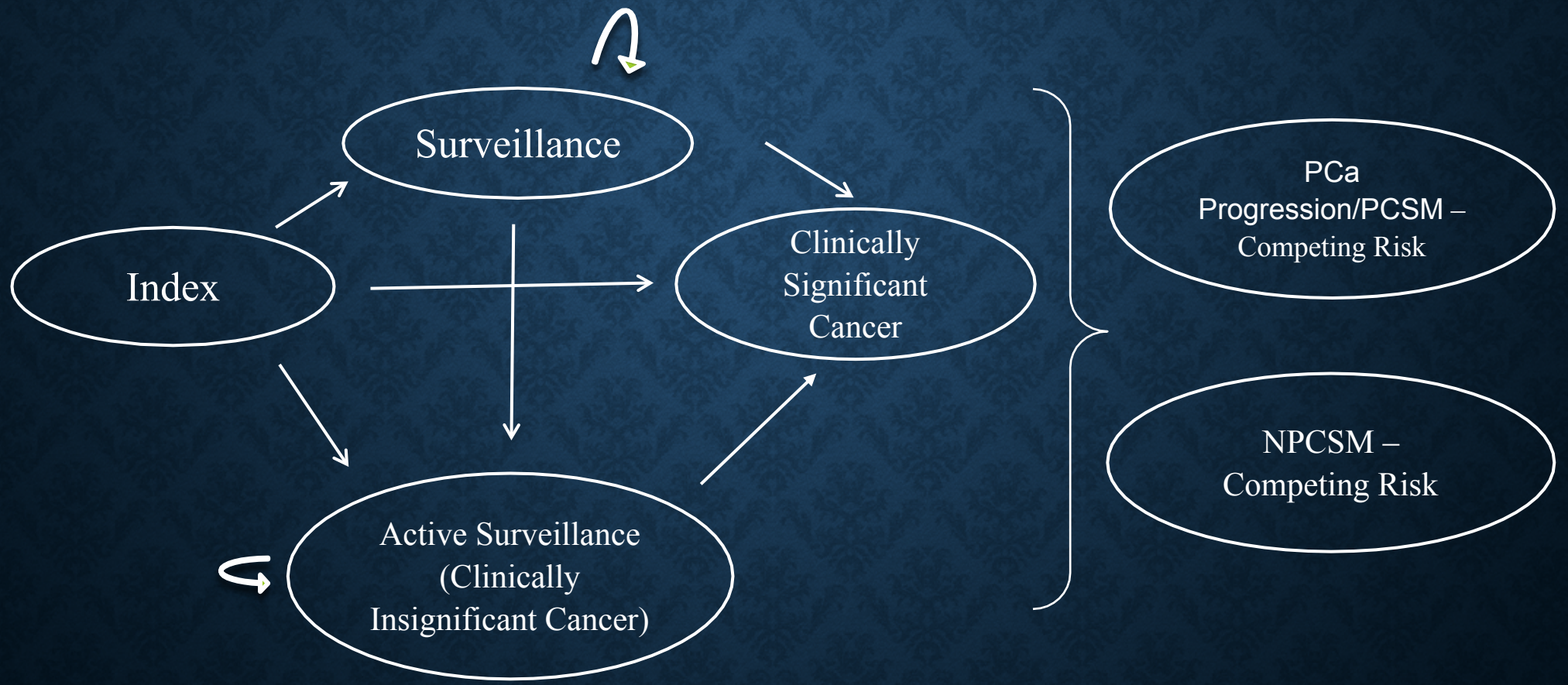
- Is MRI and biomarker testing cost-effective versus traditional systematic biopsy in the detection of prostate cancer in patients with a previous negative biopsy who are now returning for clinical suspicion of prostate cancer?

- Primary Outcome: Number of detected cases of clinically significant prostate cancer detected
- Secondary Outcomes: Time to diagnosis of clinically significant prostate cancer, number of cases of clinically insignificant prostate cancer detected (overdiagnosis), number of biopsies avoided (index and total), severe biopsy-related complications, prostate cancer specific mortality, competing risk mortality, total costs

MODEL ORGANIZATION

- Markov microsimulation model
- Cost-effectiveness analysis; Healthcare payer perspective
- Setting: Testing as an initial second intervention after a previous negative systematic biopsy
- Time Horizon: 5 & 10 years with quarterly surveillance
  - Patients censored at missed clinically significant metastatic PCa (PCa Progression), competing risk mortality/death
  - Patients with PCa diagnosis can still experience competing risk mortality

MODEL STRUCTURE: STATE TRANSITION DIAGRAM

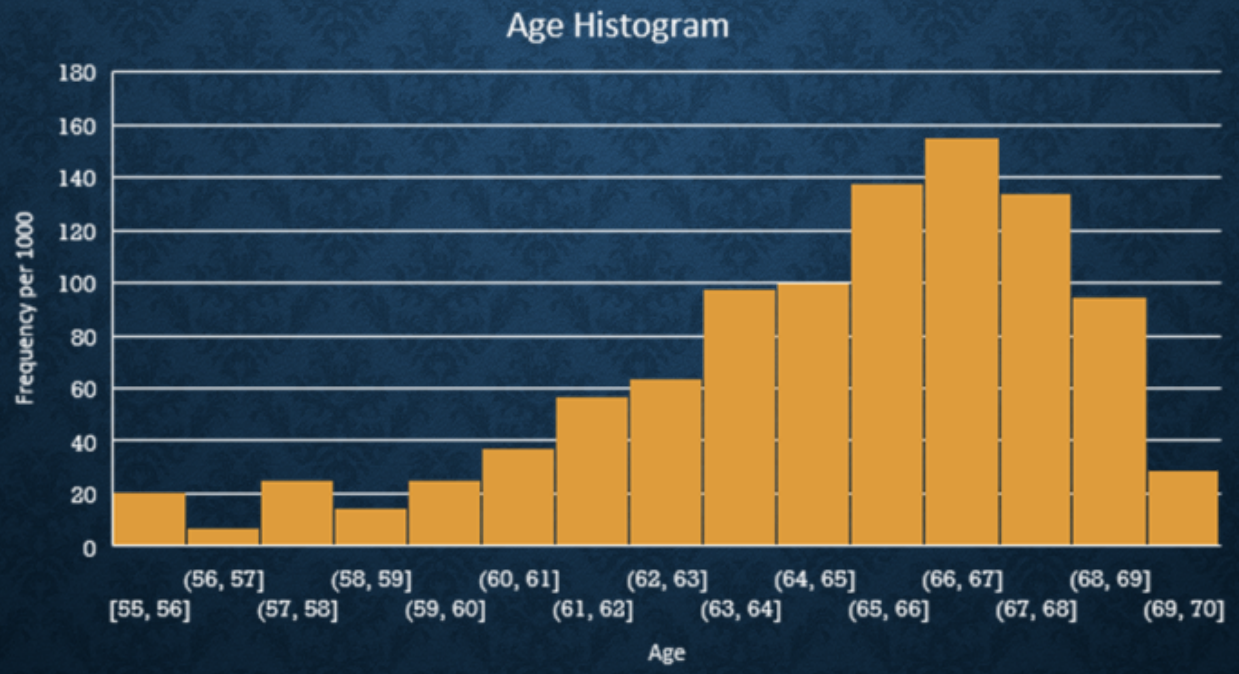


BASE CASE

- (ideally) An average male to be screened with PCa (good comorbid status, average life expectancy >10 years) and suitable for all interventions
- Representative individual level characteristics within the model:
  - Age (55-70)
  - Mean initial PSA 7.5
  - 44.3% DRE suspicious or positive
  - 9% Family History
  - Charlson comorbidity index (CCI) 0 (68%), 1 (18%), 2+ (14%)

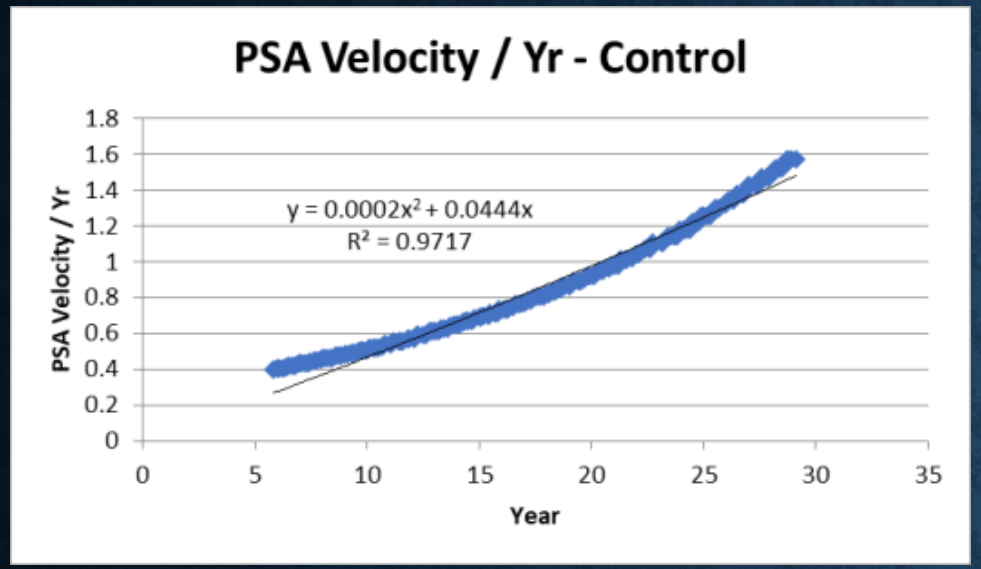
SAMPLE PATIENT INPUTS

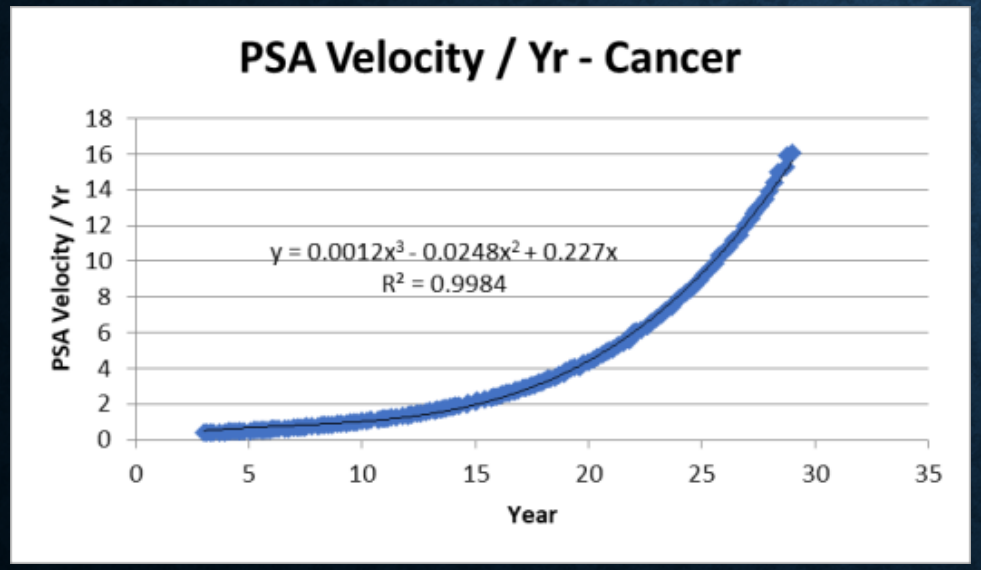
- Age

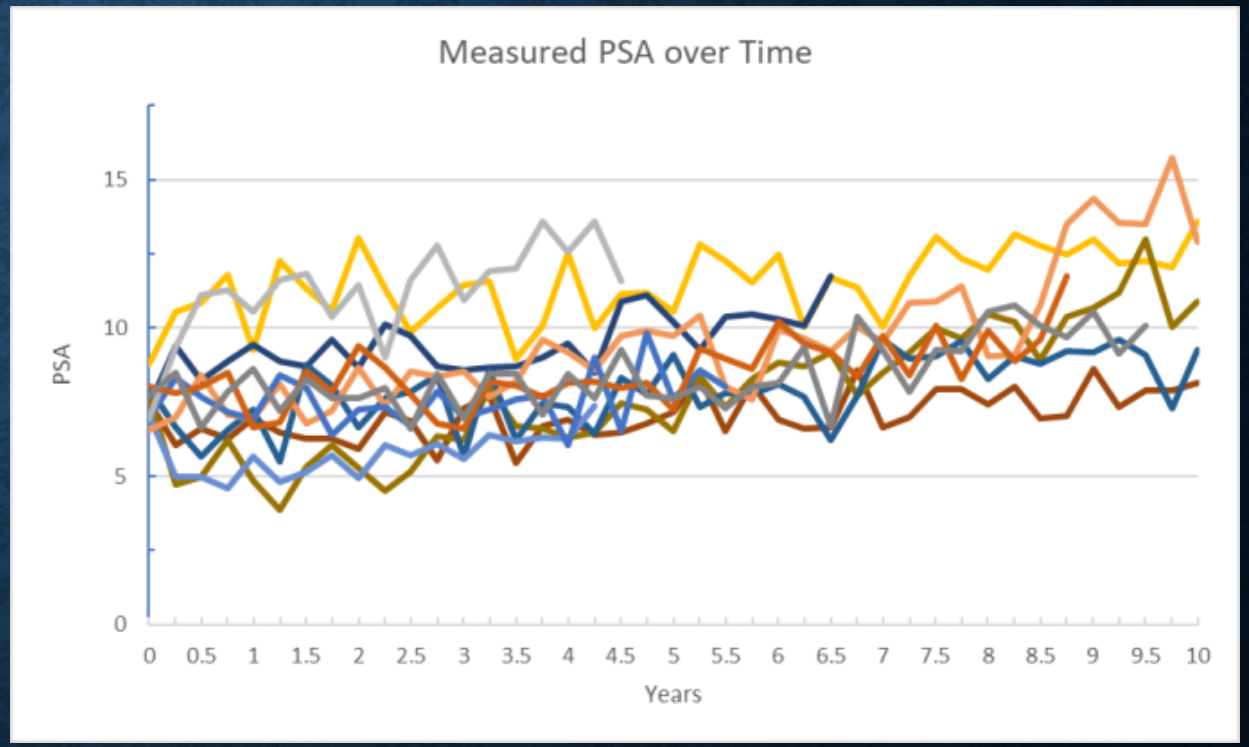


SAMPLE PATIENT INPUTS

- Individual-level modelling of PSA, velocity, and measurement error of the PSA test itself
  - Initial PSA + Velocity +/- 20% Per Cycle Variability
    (i.e. measured PSA = true PSA + ε)

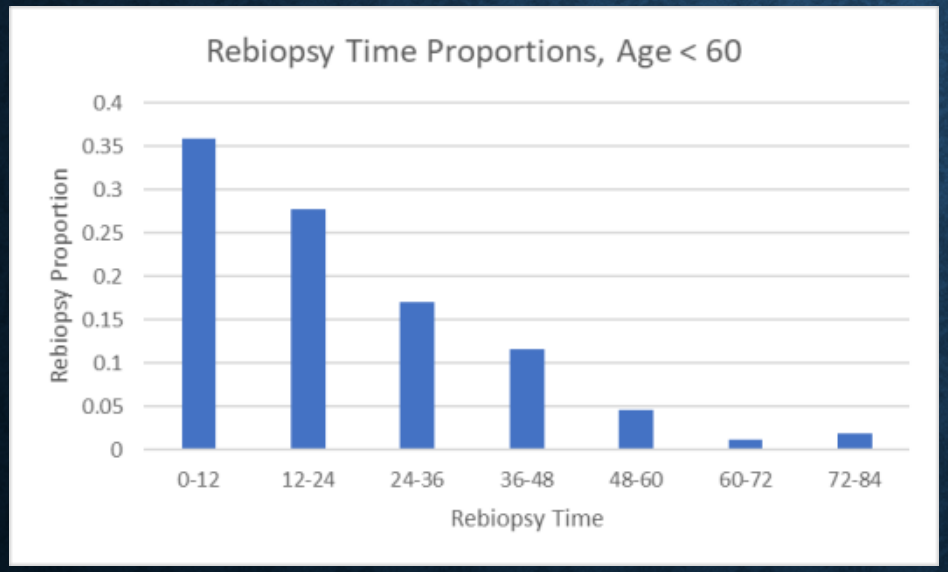

PSA Velocity / Yr - Control
PSA Velocity / Yr
y = 0.0002x² + 0.0444x
R² = 0.9717
Year

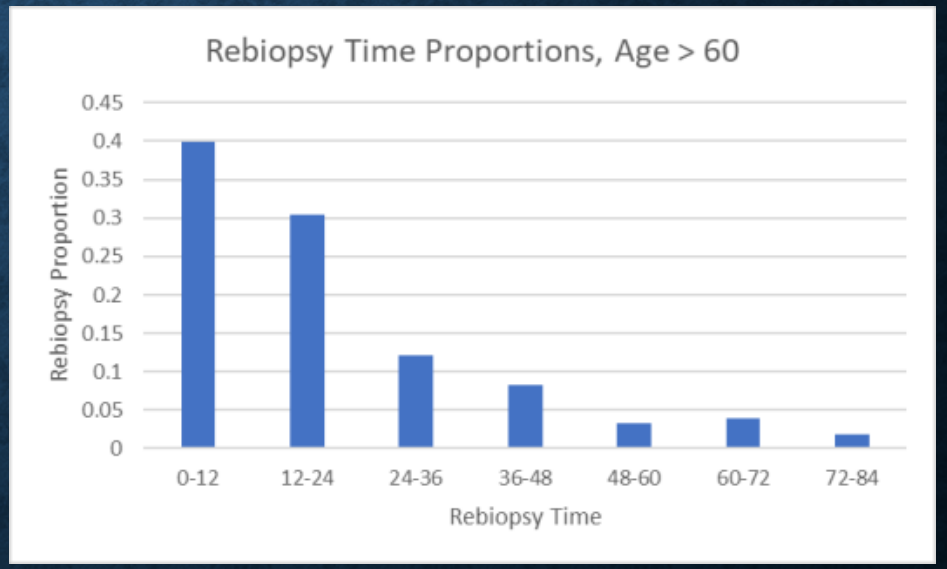

PSA Velocity / Yr - Cancer
PSA Velocity / Yr
y = 0.0012x³ - 0.0248x² + 0.227x
R² = 0.9984
Year


Measured PSA over Time
PSA
Years

SAMPLE PATIENT INPUTS

- Time since Previous Biopsy





SAMPLE TEST PERFORMANCE INPUTS

- MRI and MRI Biopsy (only cumulative sensitivity and specificities identified and calibrated against these)

Parameter	Value	Distribution
MRI: PI-RADS 3+[1]		
Sensitivity	0.745 (38/51)	Beta
Specificity	0.456 (26/57)	Beta
MRI: PI-RADS 4+[1]		
Sensitivity	0.510 (26/51)	Beta
Specificity	0.860 (49/57)	Beta

SAMPLE TEST PERFORMANCE INPUTS

Parameter	Value	Distribution
4K Score		
Sensitivity CS	0.9481 (80.6/86)	Beta
Sensitivity NCS	0.8159 (13.2/17)	Beta
Specificity	0.3801 (4.3/10.7)	Beta
PHI		
Sensitivity CS	0.9137 (239.6/263.1)	Beta
Sensitivity NCS	0.8828 (39.1/45.2)	Beta
Specificity	0.2940 (9.4/30.5)	Beta

Parameter	Value	Distribution
Rate of PCa Clinical Progression[1,2,3]	22.89/1000 person-years (112/4893)	Beta
Gleason Adjustor[4]	Gleason 3+4: Prostate Cancer Subdistribution Hazard Ratio: 1.32 (1.06-1.65) Gleason 4+3: Prostate Cancer Subdistribution Hazard Ratio: 1.73 (1.36-2.19) Gleason 8: Prostate Cancer Subdistribution Hazard Ratio: 2.10 (1.63-2.69) Gleason 9/10: Prostate Cancer Subdistribution Hazard Ratio: 3.93 (3.15-4.89)	LogNormal
Rate of Non PCa Specific Mortality[3,5]	18.13/1000 person-years (178/9804)	Beta
CCI Adjustor[4] (reference: CCI 0)	CCI 1: Prostate Cancer Subdistribution Hazard Ratio: 0.79 (0.50-1.23) Other Mortality Subdistribution Hazard Ratio: 2.07 (1.51-2.85) CCI 2+: Prostate Cancer Subdistribution Hazard Ratio: 0.97 (0.59-1.59) Other Mortality Subdistribution Hazard Ratio: 2.34 (1.59-3.44)	LogNormal
Age Adjustor Fractional Polynomial[4,6]	Prostate Cancer Subdistribution Hazard Ratio: 1.003 (1.002-1.003) Other Mortality Subdistribution Hazard Ratio: 1.13 (1.12-1.14)	LogNormal

SAMPLE MODEL INPUTS

Mortality and Progression Characteristics

BASE CASE RESULTS

Results	MRI PI-RADS 3+	MRI PI-RADS 4+	Systematic Biopsy	PHI	PCA3
% CS Detected	**31.68%**	**26.93%**	**26.25%**	**20.80%**	**23.31%**
Cost ($)	**$2,379.44**	**$2,146.80**	**$2,238.48**	**$2,156.01**	**$2,108.81**
Index Biopsies Avoided	35.87%	67.97%	0%	69.26%	55.46%
Complications (Sepsis)	2.71%	2.19%	3.58%	2.28%	2.50%
Mean Time to CS Detection	7.00 months	12.94 months	13.96 months	25.3 months	19.7 months
PCa Progression	2.41%	3.02%	3.10%	3.73%	3.48%

MRI AT PI-RADS 4+ DOMINATES SYSTEMATIC BIOPSY:

INCREASED ABSOLUTE CS CANCER DETECTION
AVOIDED 68% OF BIOPSIES
COST-SAVINGS

Results	MRI PI-RADS 4+	Systematic Biopsy	Difference
% CS Detected	26.93	26.25%	+0.68%
Cost ($)	$2,146.80	$2,238.48	$91.6 saved
Index Biopsies Avoided	67.97%	0%	67.97% avoided
Complications (Sepsis)	2.19%	3.58%	-1.39%
Mean Time to CS Detection	12.94 months	13.96 months	-1.02 months earlier
PCa Progression	3.02%	3.10%	-0.08%

MRI AT PI-RADS 4+ VS 3+ TRADE-OFF:

DECREASED ABSOLUTE CS CANCER DETECTION VS INCREASED BIOPSY AVOIDANCE AND COST SAVINGS

Results	MRI PI-RADS 4+	MRI PI-RADS 3+	Difference
% CS Detected	26.93	31.68%	-4.75%
Cost ($)	$2,146.80	$2,379.44	$232.64 saved
Index Biopsies Avoided	67.97%	35.87%	32.1% avoided
Complications (Sepsis)	2.19%	2.71%	-0.52%
Mean Time to CS Detection	12.94 months	7.00 months	+5.94 months later
PCa Progression	3.02%	2.41%	+0.61%

RESULTS MAINTAINED IN SCENARIO ANALYSIS: 10 YEAR (5-YEAR)

Results	MRI PI-RADS 3+	Systematic Biopsy	Difference
% CS Detected	37.39% (31.68%)	34.55% (26.25%)	2.84%
Cost ($)	$3,331.64 ($2,379.44)	$3,232.54 ($2,238.48)	$99.09
Mean Time to CS Detection	19.10 (7.00) months	30.65 (13.96) months	-11.56 months
Complications	4.09% (2.71%)	5.10% (3.58%)	-1.01%
PCa Progression	5.27% (2.41%)	6.23% (3.10%)	-0.96%

CONCLUSIONS

- MRI is cost effective versus systematic biopsy
  - Dominates at the PI-RADS 4+ threshold with improved detection of clinically significant PCa while cost-saving
- Clinical trade-off seen from adding PI-RADS 3 lesions: further increase in clinically significant PCa detection but at a higher cost and more biopsies