

Active Surveillance at Johns Hopkins – Update 2015




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Disclosure

NONE



**REGISTER
TODAY**

 **IPCU**

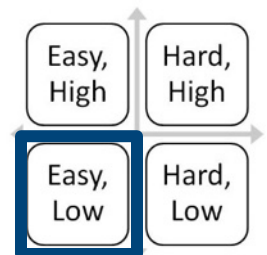
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INTERNATIONAL PROSTATE CANCER UPDATE

Cascade Conference Center Vail, Colorado

Active Surveillance: A Strategy for Reducing Over Treatment of Prostate Cancer

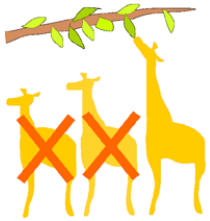
- Management option for men with localized prostate cancer who are *fit* for curative intervention
- Selection of men at *low risk* of harm without treatment
- Possible delayed *curative intervention* for those with disease reclassification (“progression”)
- Low Risk –vs- Very Low Risk



How often are “Life Threatening” Cancers Misclassified as Insignificant

Pathological Feature*	Cases Predicted to be Insignificant #(%) by	
	Modified Epstein criteria (Kryvenko et al, Urology 2014)	mMRI (Turkbey et al, Radiology 2013)
Gleason score 3+4 non organ confined, or any $\geq 4+3$, and/or seminal vesicle invasion	Caucasians 4/185 (2%)	4/133 (3%)
	AA's 3/62 (5%)	





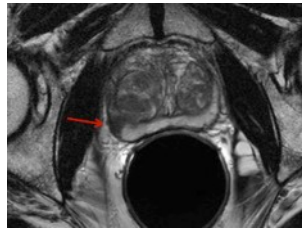
Multi-parametric MRI in Active Surveillance

- Selection- reduction of grade misclassification
 - mMRI fusion biopsy has higher sensitivity for high grade cancer as compared to TRUS guided systematic biopsies

Turkbey, Mani 2011; Hambrock, Hoeks 2012; Siddiqui, Rais-Bahrami 2013

- Monitoring- reduction of surveillance biopsies
 - mMRI has high negative predictive value for reclassification events

Fradet, Kurhanewicz 2010; Mullins, Bonekamp 2013; Hoeks, Somford 2013



Selection for Active Surveillance: Johns Hopkins



RISK		TUMOR	PATIENT	OTHER
Very low	PSA < 10	Stage T1c and, PSA density < 0.15 and, Biopsy: Gleason < 7, < 3 cores, unilateral	Life expectancy < 20y, surveillance <i>preferred</i>	MRI optional
	PSA 10-20	Same but PSA density < 0.1		MRI
Low		Stage T1c/T2a and, Gleason < 7 and, PSA < 10	Life expectancy < 10y, surveillance <i>preferred</i> Age > 65y	MRI
Intermediate		T2b/T2c or, Gleason 3+4 or, PSA 10-20	Life expectancy < 10y	MRI (?)

Monitoring of men in Active Surveillance



TEST	INTERVAL
DRE and PSA	6 months
12-14 core biopsy	<u>Annual</u> 1) not very low risk and >10y life expectancy 2) very low risk, PSA>10
	<u>Biennial</u> 1) very low risk and no MRI suspicion
	<u>Not indicated</u> 1) age >75y and no MRI suspicion
MRI	Biennial with targeting of suspicious lesions (MRI/TRUS fusion)

Triggers for Curative Intervention in Active Surveillance

TRIGGER
WARNING

CRITERIA FOR CURATIVE INTERVENTION

Patient preference

Reclassification of risk:

- Very low to low risk, life expectancy >20y

Gleason

- Any pattern 4, life expectancy >10y
- $\geq 4+3$, life expectancy >5y

PSA

- 10-20 and not very low risk
- >20

Active Surveillance : Johns Hopkins Program

1368 men recruited since 1995

Follow-up

median 5y (IQR 2-7)

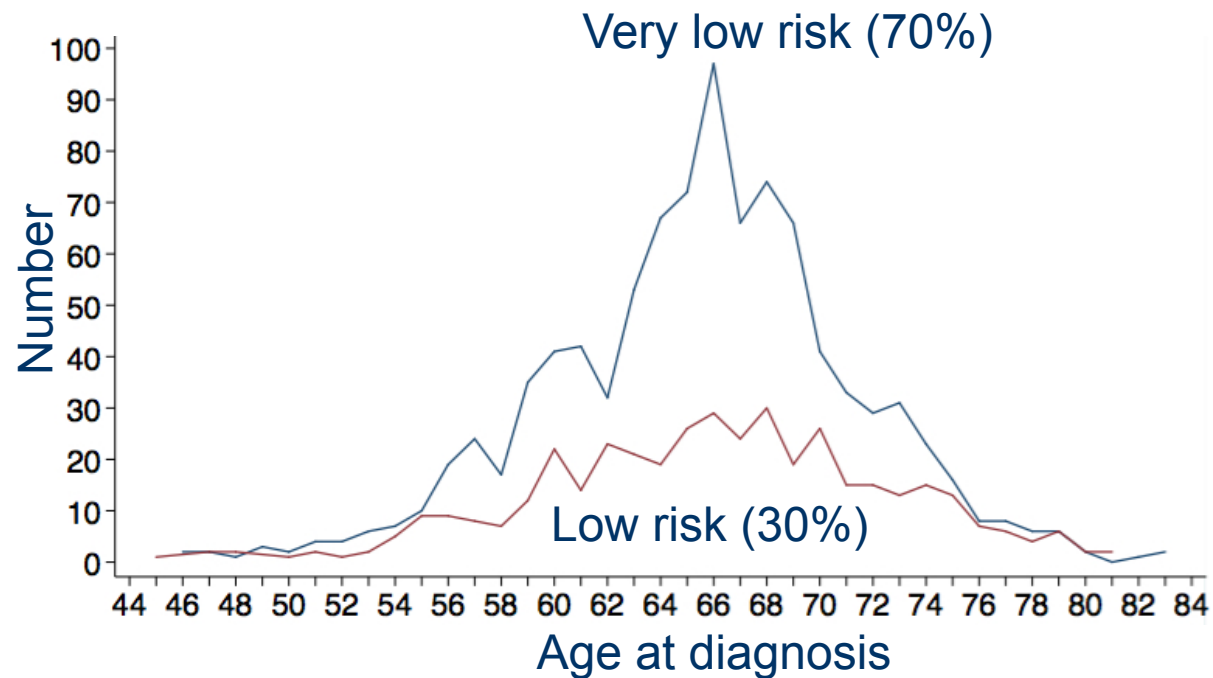
6,766 person years

DRE/PSA biannual

biopsy 1-2yrs

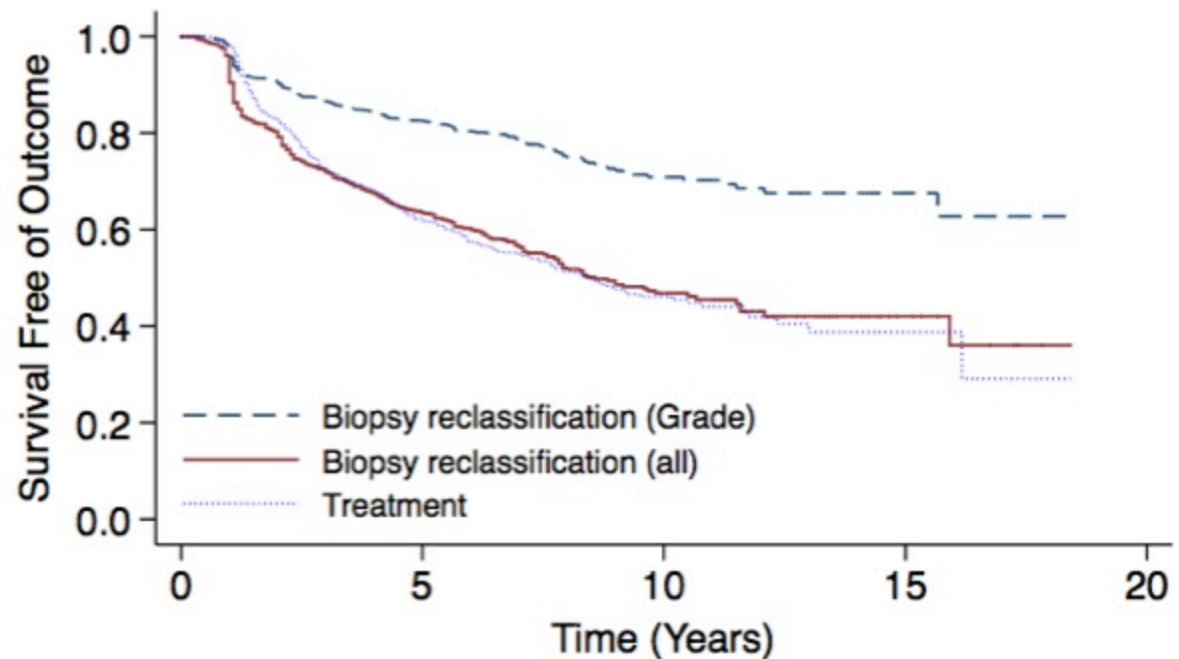
Trigger for intervention

-biopsy reclassification



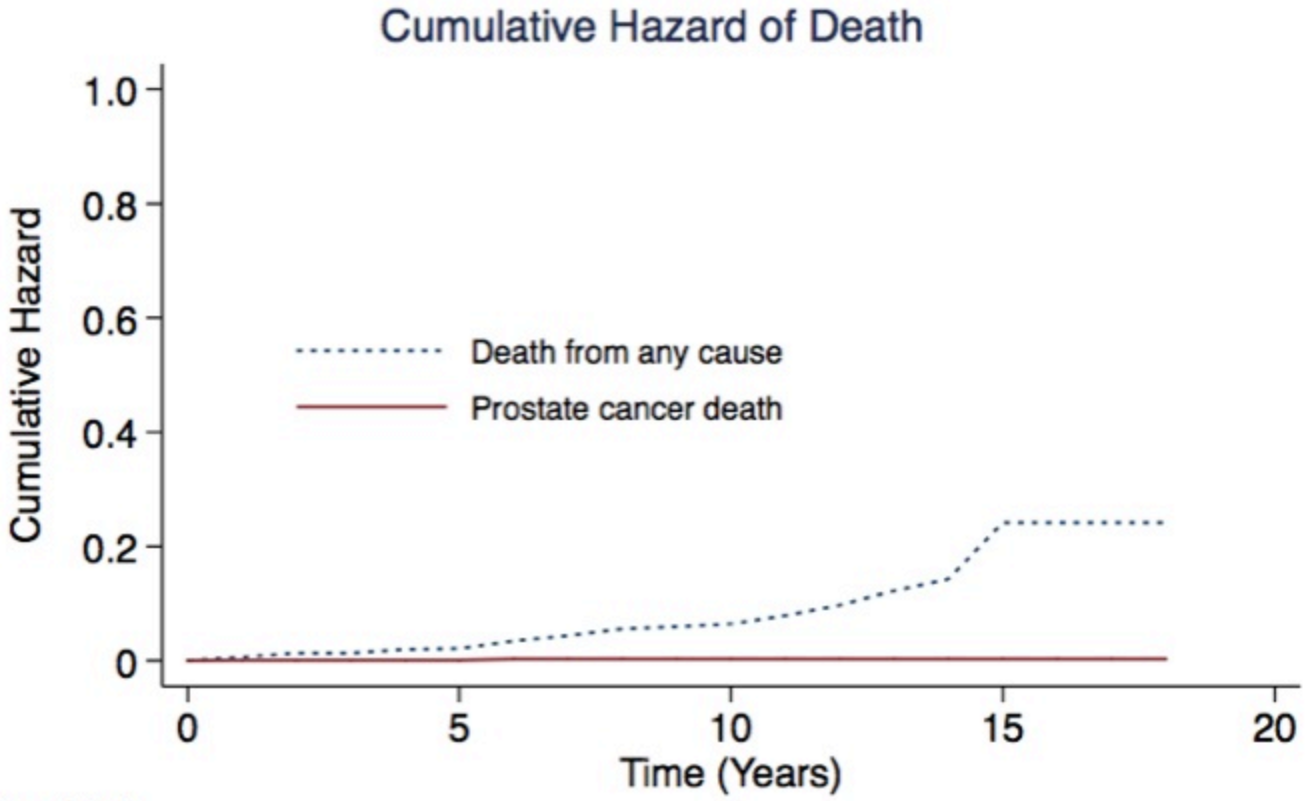
Active Surveillance at Johns Hopkins

AS Outcomes



	No. at risk				
Biopsy reclassification (Grade)	1298	539	125	19	0
Biopsy reclassification (all)	1298	441	86	10	0
Treatment	1298	412	73	8	0

Active Surveillance at Johns Hopkins



	0	5	10	15	20
No. at risk	1298	650	184	26	0
Death from any cause	1298	650	184	26	0
Prostate cancer death	1298	650	184	26	0

Fluoroquinolone Resistance in the Rectal Flora of Men in an Active Surveillance Cohort: Longitudinal Analysis

Jason E Cohen, Patricia Landis, Bruce Trock,
Hiten D Patel, Mark W Ball, Edward Schaeffer,
Ballentine Carter



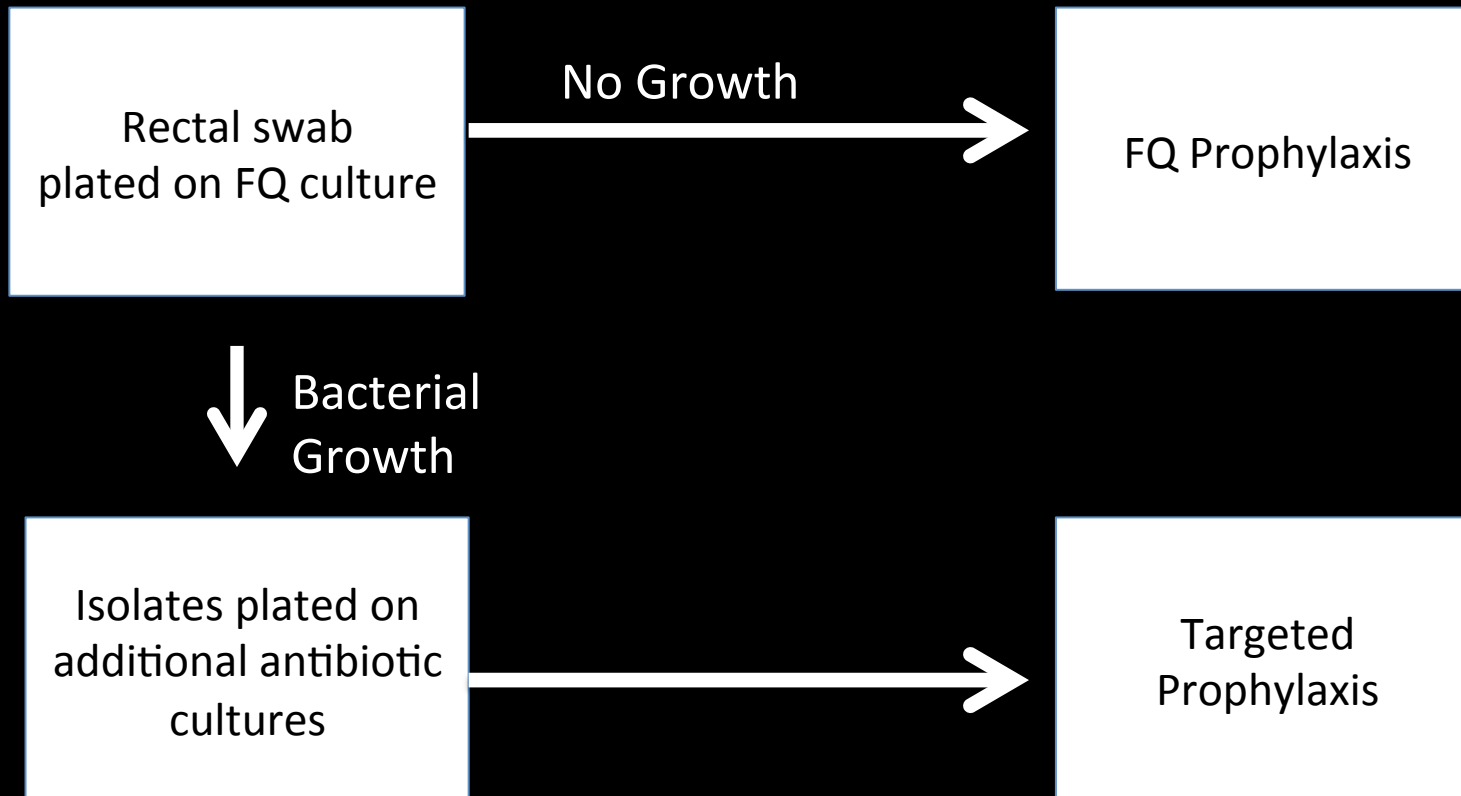
Brady Urological Institute
Johns Hopkins University

AUA 2014 Presentation

Rise of Infectious Complications

- Rising rates of infection related hospitalizations
- Increase most likely due to FQ resistance in rectal flora
- Resistance rates
 - 10-22% of men undergoing TRUS Bx have resistance to FQ
- Associated with resistance
 - Diabetes, Heart Valve Replacement, FQ use in past 3 months
- Longitudinal trends in resistance within an individual have not been characterized

Microbiology Assay



Methods

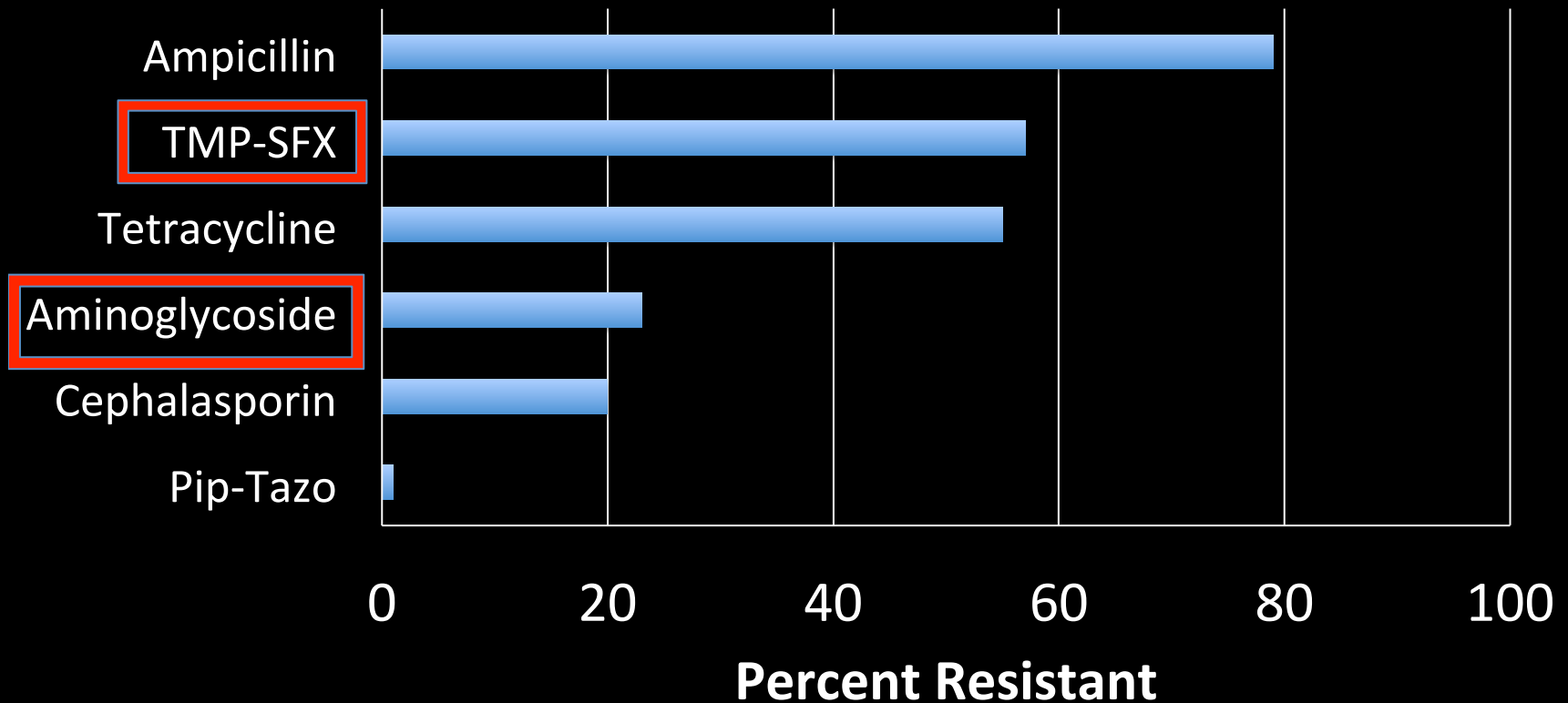
- Study cohort (men with rectal swabs)
 - Men in AS retrospectively queried for resistance profiles, demographic, medical data, biopsy history
- Comparison group
 - Men presenting for diagnostic prostate biopsy during same time period/setting

Results

	Active Surveillance	Comparison Cohort	p-value
Median Age (IQR)	65.9 (62.4-69.2)	63 (58-68)	—
Number of Cultures	416	221	—
Number Resistant (Percent)	105 (25.2%)	54 (24.4%)	0.824

Antibiotic Sensitivities among men with Fluoroquinolone Resistance in AS

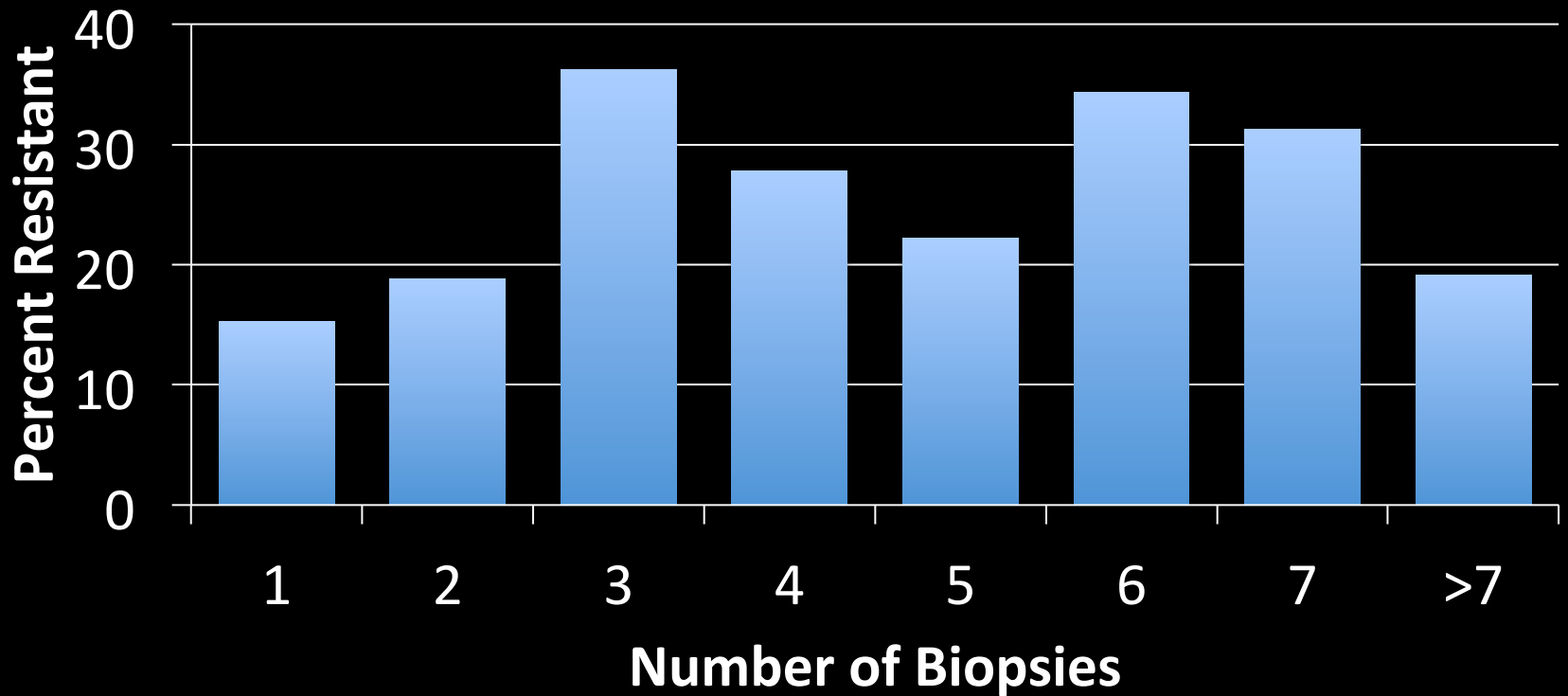
Resistance Profile



Association of Resistance and Biopsy History in AS Cohort

	FQ Sensitive	FQ Resistant	p-value
Median time (IQR) from biopsy to swab (months)	8 (6,13)	10 (6,17)	0.984
TRUSBx in Past 12 Months (Percent)	70%	68%	0.804
TRUSBx in Past 6 Months (Percent)	33%	35%	0.691

Resistance Does Not Increase with Increasing Biopsy Number

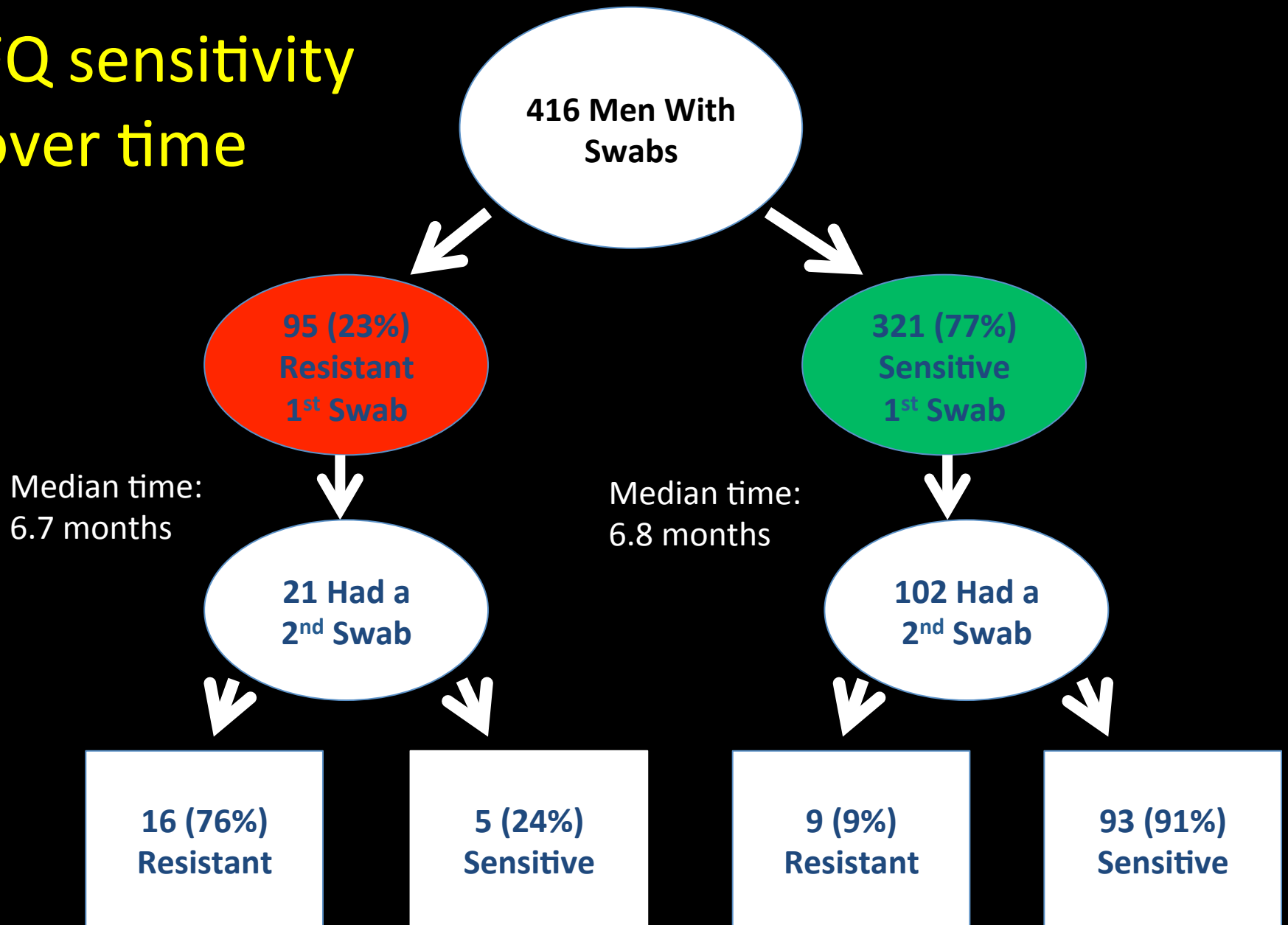


	FQ Sensitive	FQ Resistant	p-value
Median number of TRUSBx (IQR) before swab	3.5 (2,6)	4.0 (3,6)	0.106

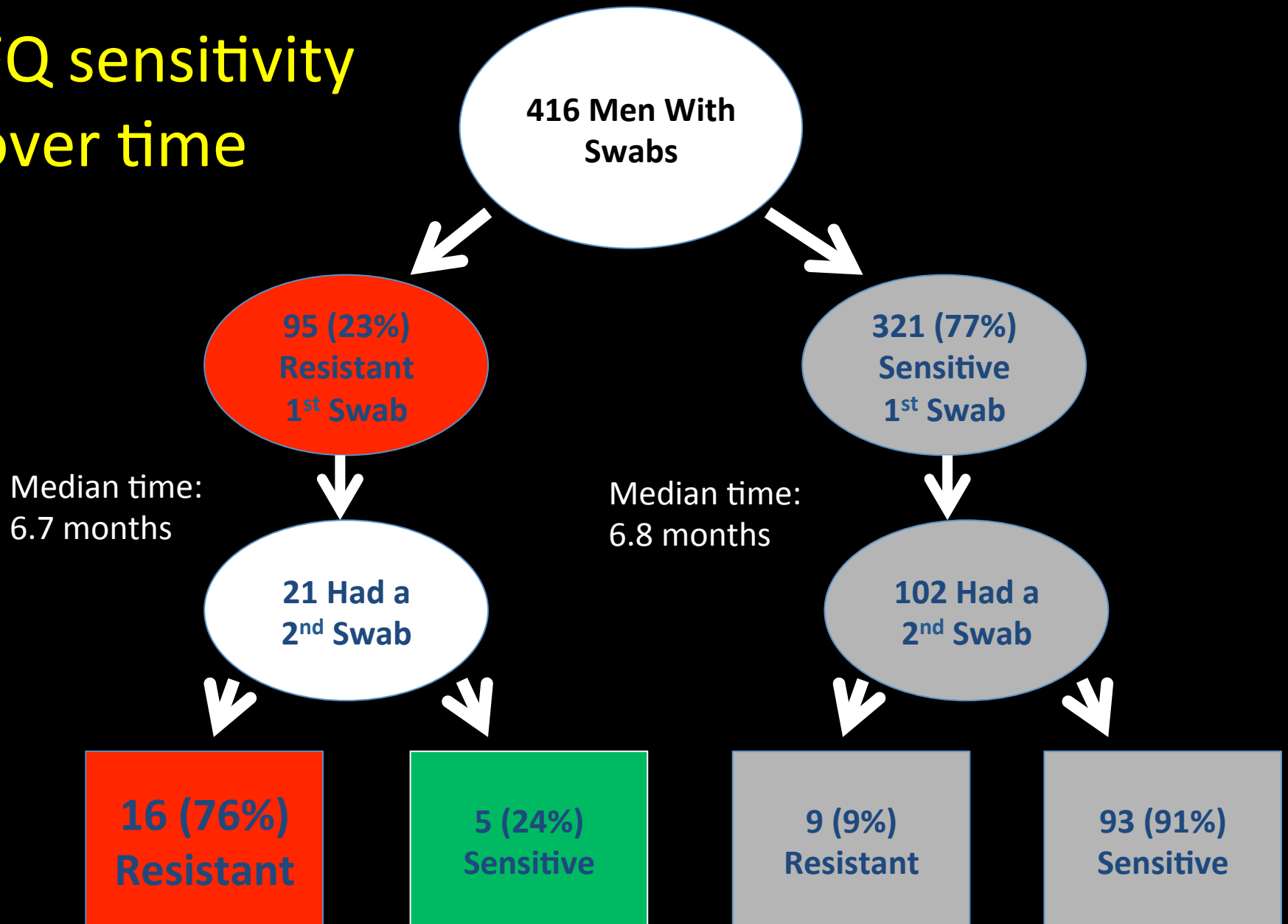
Factors Associated with FQ Resistance in AS Cohort

- Age, PSA, Prostate volume, HTN, Cholesterol, Heart Disease, Urologic History, Previous Biopsy
 - Not associated with resistance
- **Diabetes was only significant finding associated with resistance**
 - 4.5% in FQ sensitive v. 15.7% in FQ resistant, $p = 0.0007$
- **Multivariate Analysis**
 - Diabetes OR=3.98 (95% CI: 1.71, 9.29), $p=0.001$

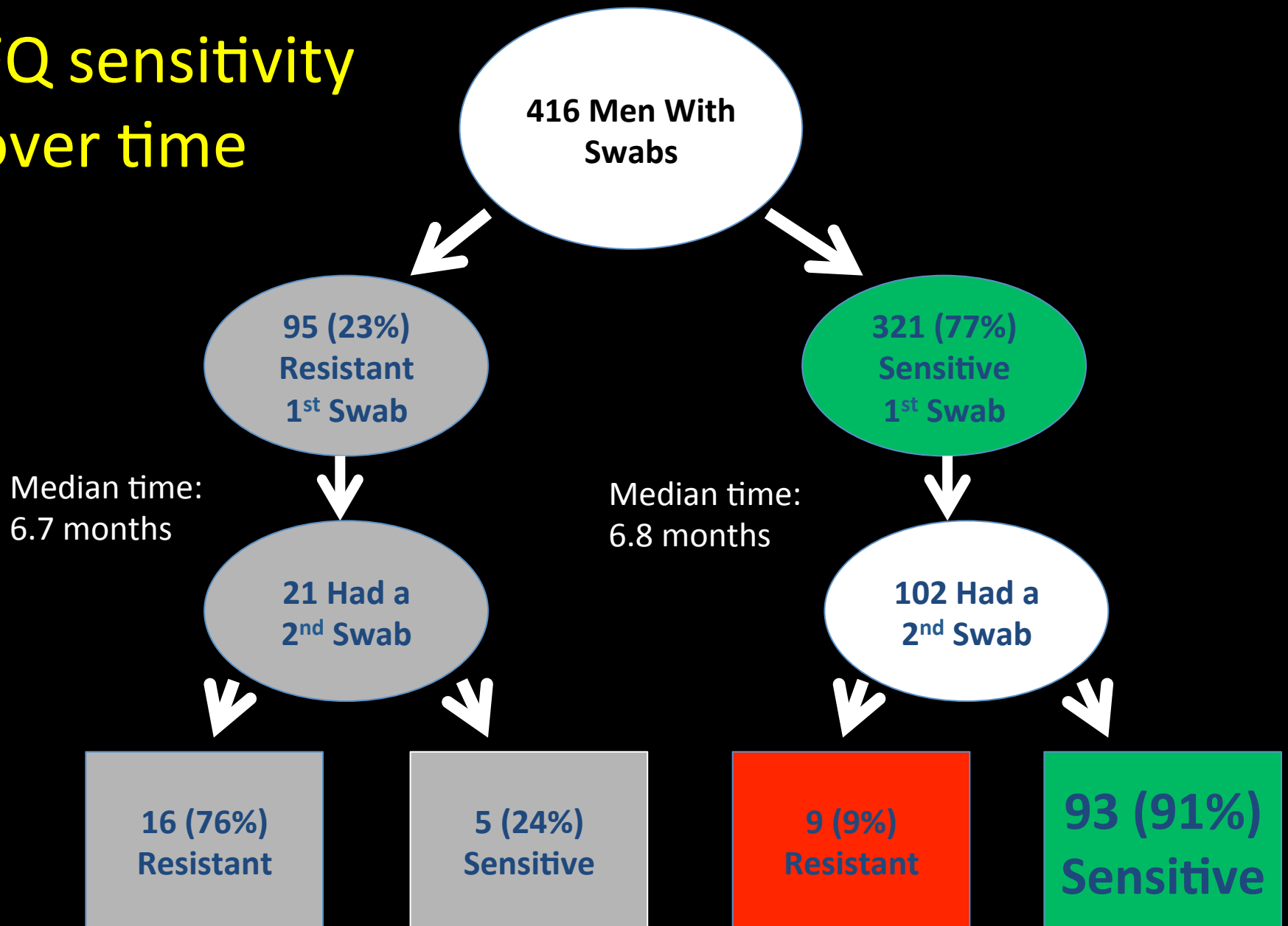
FQ sensitivity over time



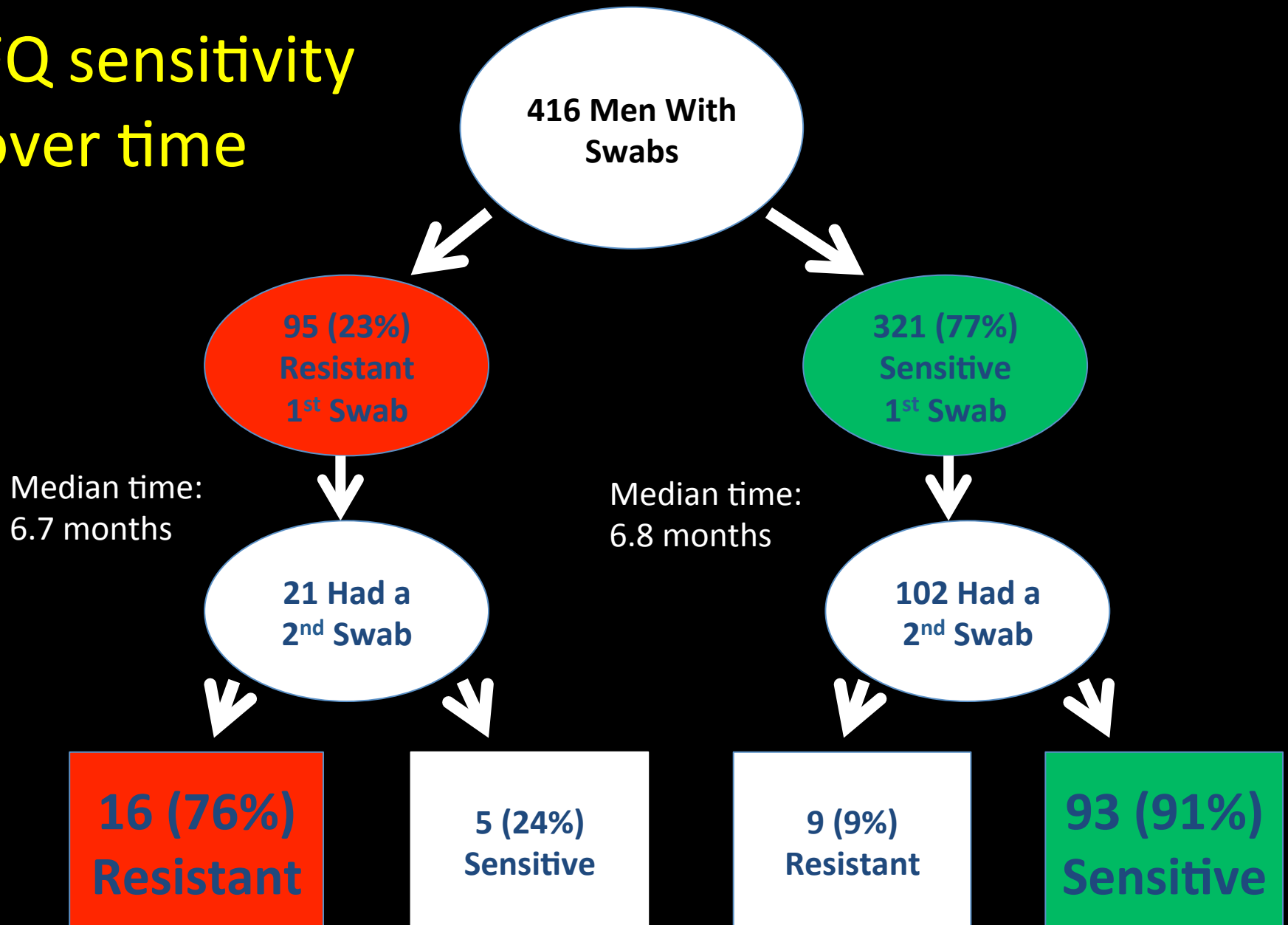
FQ sensitivity over time



FQ sensitivity over time



FQ sensitivity over time



Conclusions

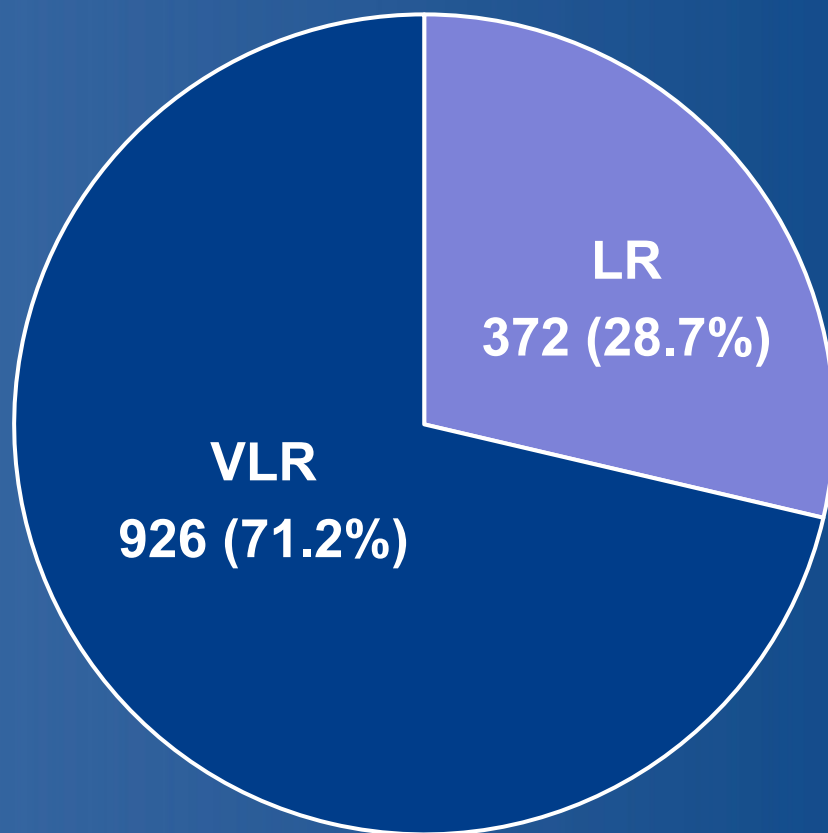
- 1 in 4 men presenting for prostate biopsy at Johns Hopkins have FQ resistant flora
- Resistance rates are not higher among men in AS as compared to men undergoing diagnostic biopsies
- Multiple biopsies were not associated with increased FQ resistance
- Diabetes is a risk factor for FQ resistance
- Most men that carry FQ resistant flora remain resistant over time

Johns Hopkins AS Program

- Initiated in 1995
- 1,298 men enrolled as of September 2014
- Median follow up: 5.0 years (0.01-18.0)
- 6,766 person-years of follow up
 - Men followed for 5+ years: 650
 - Men followed for 10+ years: 184
 - Men followed for 15+ years: 26

Johns Hopkins AS Program

Subjects by Risk Classification



Results – Primary Outcomes

Proportion and cumulative incidence in favorable-risk men

	N (%)	10-year	15-year
Death, all-cause	49 (3.8)	6.8%	31.3%
PCa death	2 (0.15)	0.1%	0.1%
PCa death or metastasis	5 (0.4)	0.6%	0.6%

Results – Secondary Outcomes

Proportion and cumulative incidence in favorable-risk men

	N (%)	5-year	10-year	15-year
Any reclassification	467 (36)	35%	49%	56%
Grade reclassification	233 (18)	17%	26%	31%
Curative treatment	471 (36)	37%	50%	57%

Conclusions

- Men with favorable risk disease considering AS should be informed that over 10 to 15 years there is a:
 - low risk (4-6%) of reclassification to high grade ($GS \geq 4+3$) cancer
 - low risk (<1%) of PCa death or metastasis
- More restrictive inclusion criteria (Toronto –vs- Hopkins) and more intensive monitoring appear to be associated with:
 - higher rates of treatment
 - lower rates of adverse oncological outcomes
 - With additional follow-up of this and other cohorts we will be able to better quantify the risks and benefits associated with AS

Active Surveillance Johns Hopkins

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