PASS
Prostate Active Surveillance Study

The Canary Prostate Active Surveillance Study (PASS)

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Early Detection Research Network

CANARY FOUNDATION

Canary PASS: the Beginning

Canary PASS timeline:

- June 2007:

  Canary Foundation proposal for "Early Detection" in prostate cancer

- September 2007:

  NCI EDRN collaboration formed coordinating center

- October 2007:

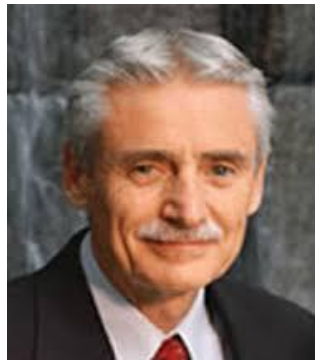
  Initial meeting to design 3 yr, 500 patient, active surveillance study

- July 2008:

  First patient enrolled

D.Listwin

L.Hartwell



P.Nelson

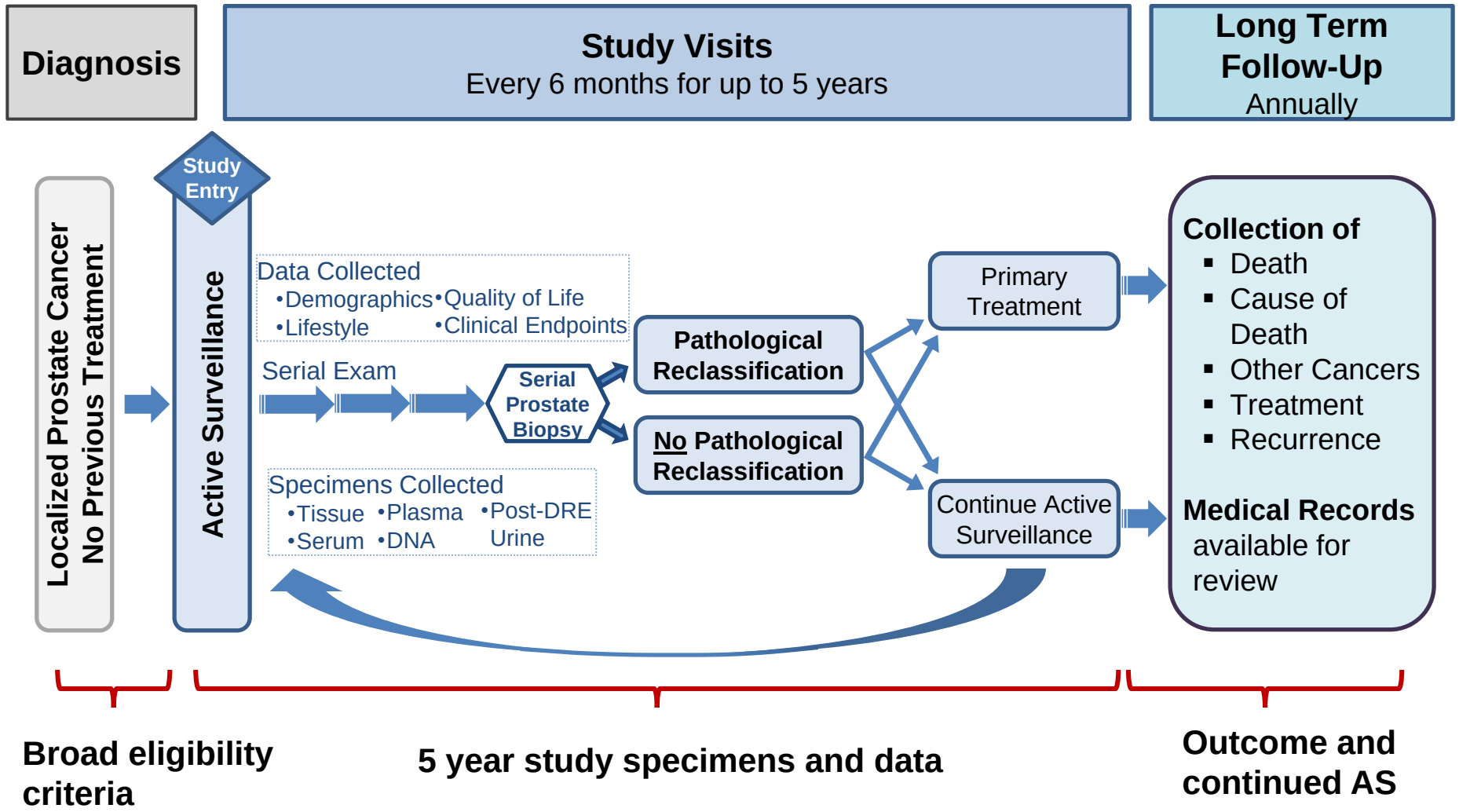
CANARY FOUNDATION

Stopping Cancer Early – The Best Possible Investment

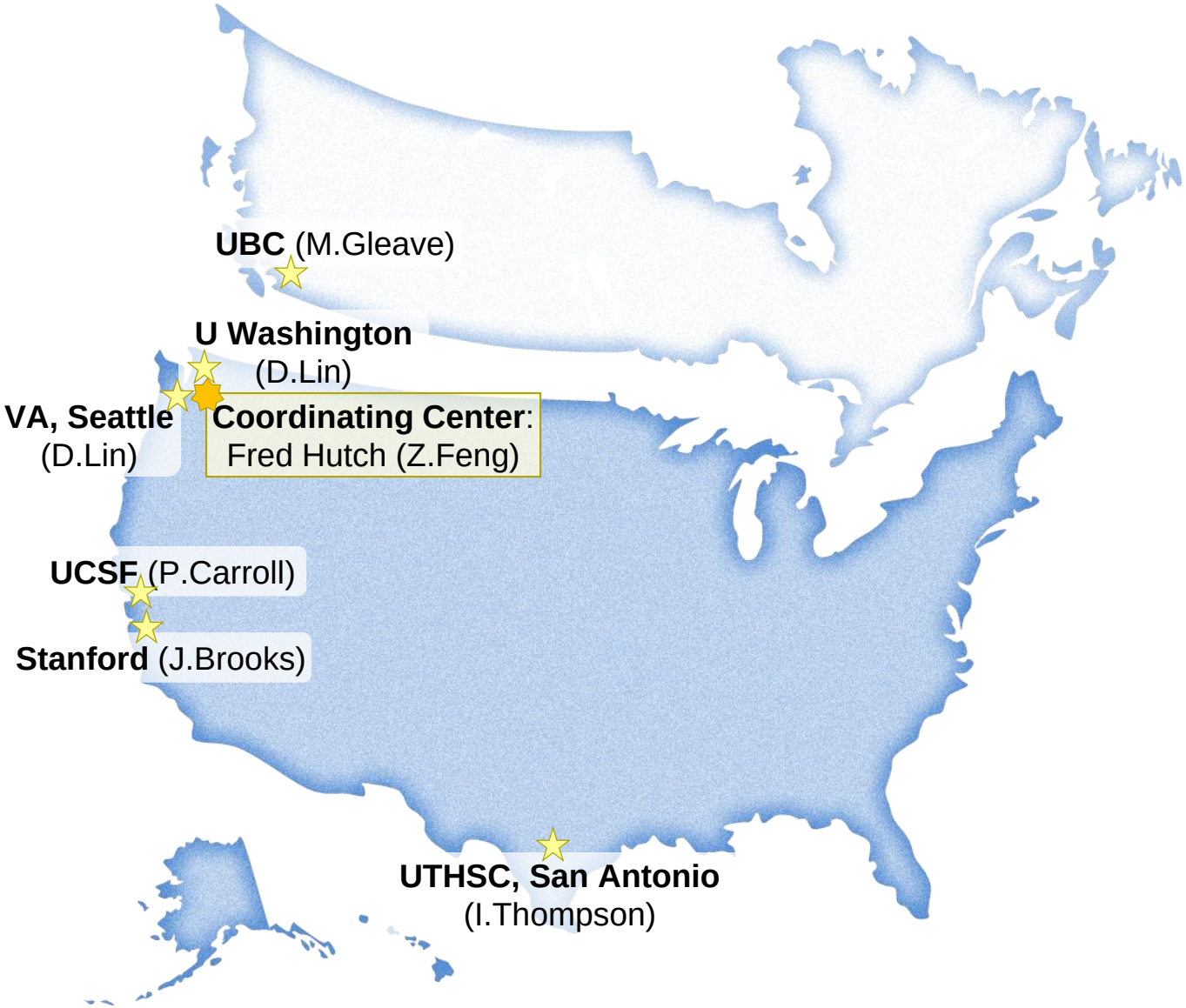
Early Detection Research Network

(2007 – 2013)

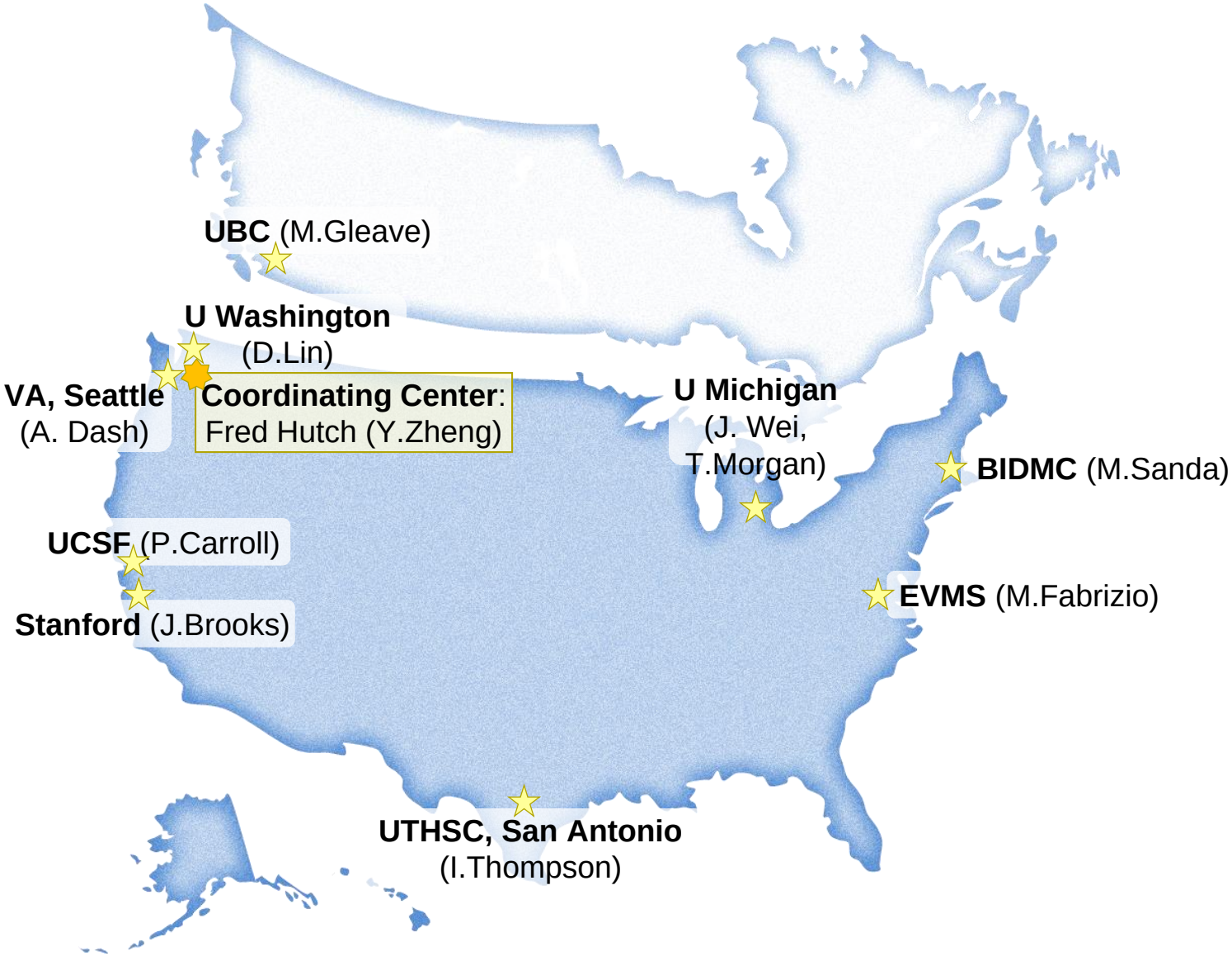
PASS Protocol



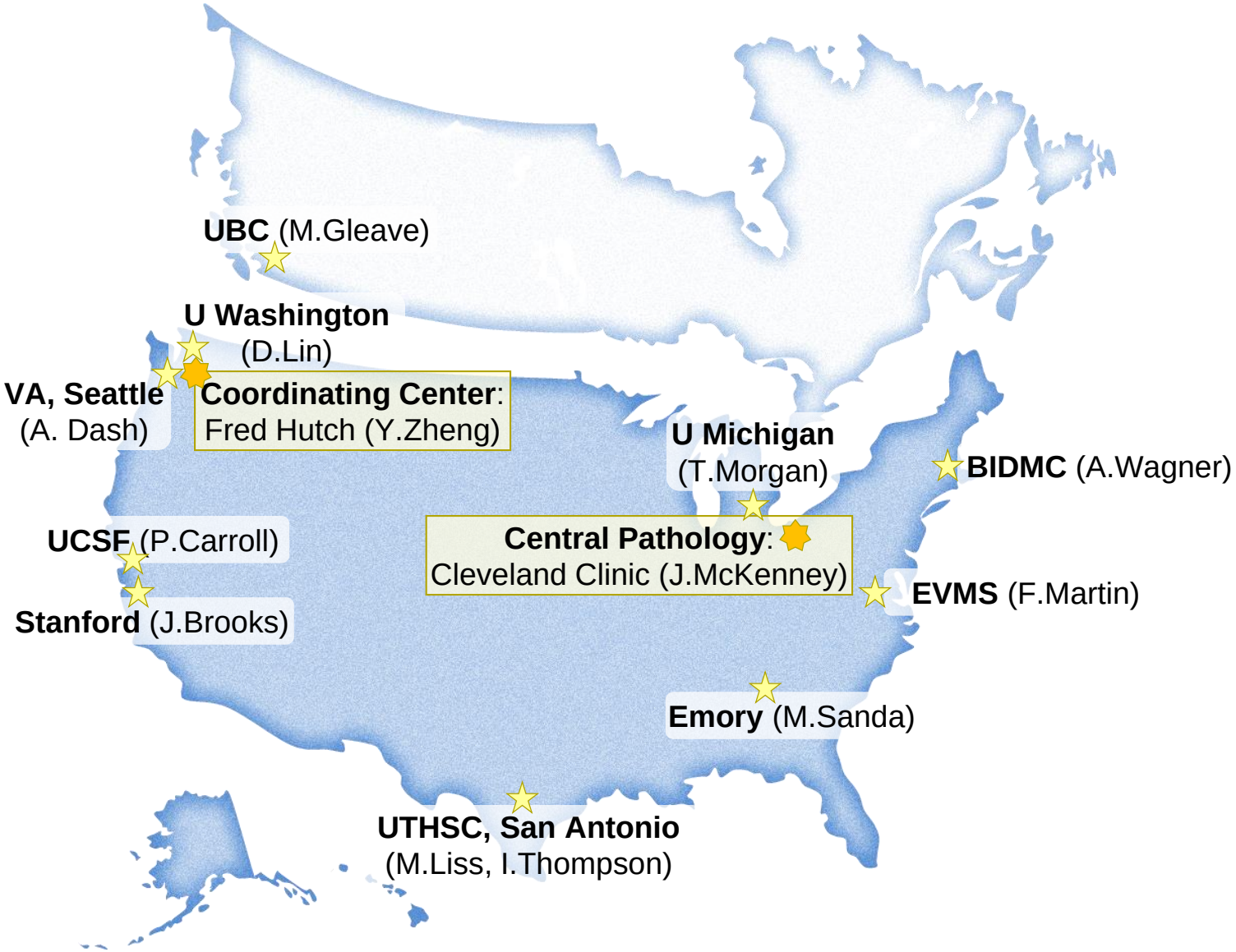
Canary PASS ~ 2007



Canary PASS 2009-2017

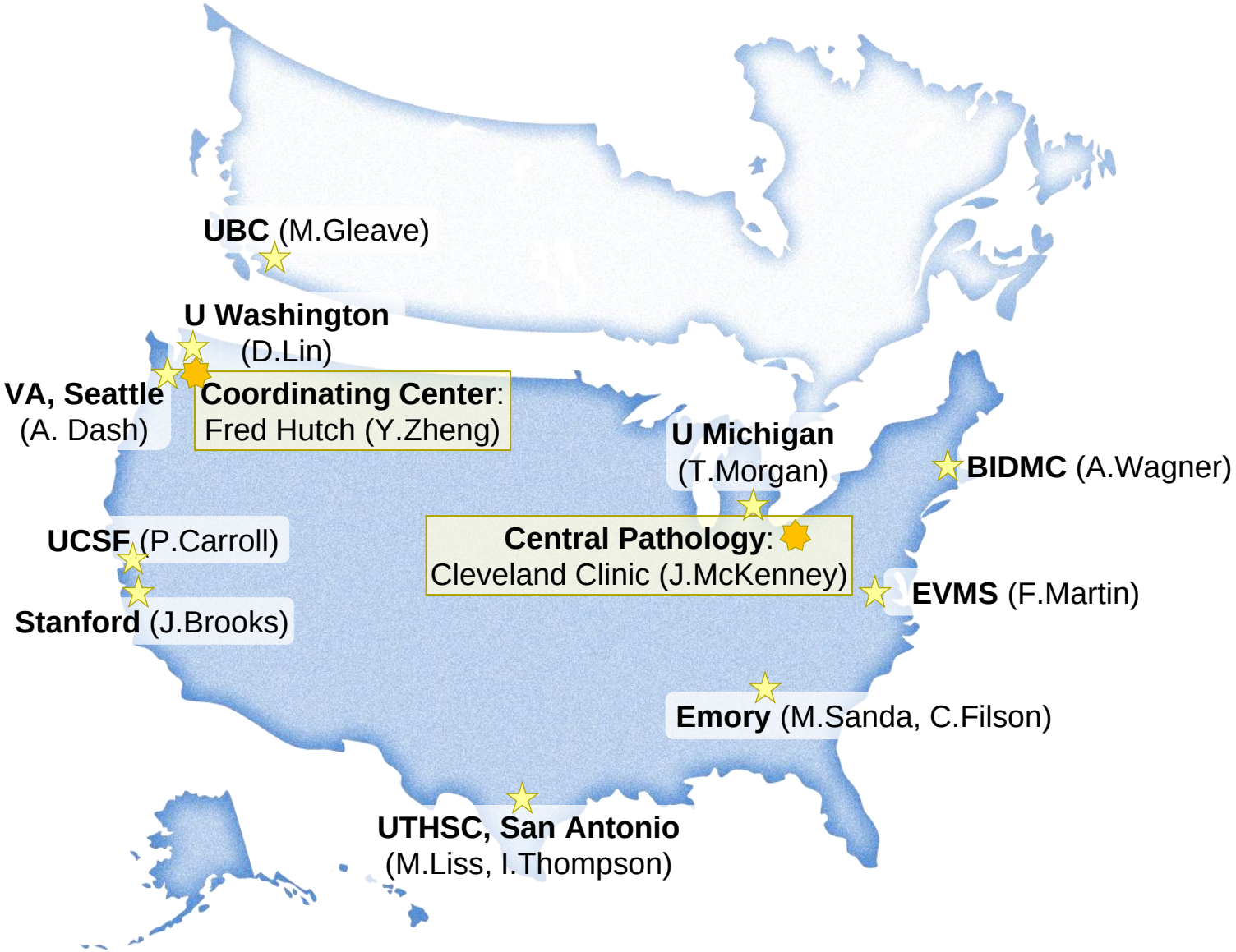


Canary PASS 2017 - present



Canary PASS (N = 2,001)

Largest Multi-site AS Study and Biorepository in North America



Prostate Cancer Active Surveillance

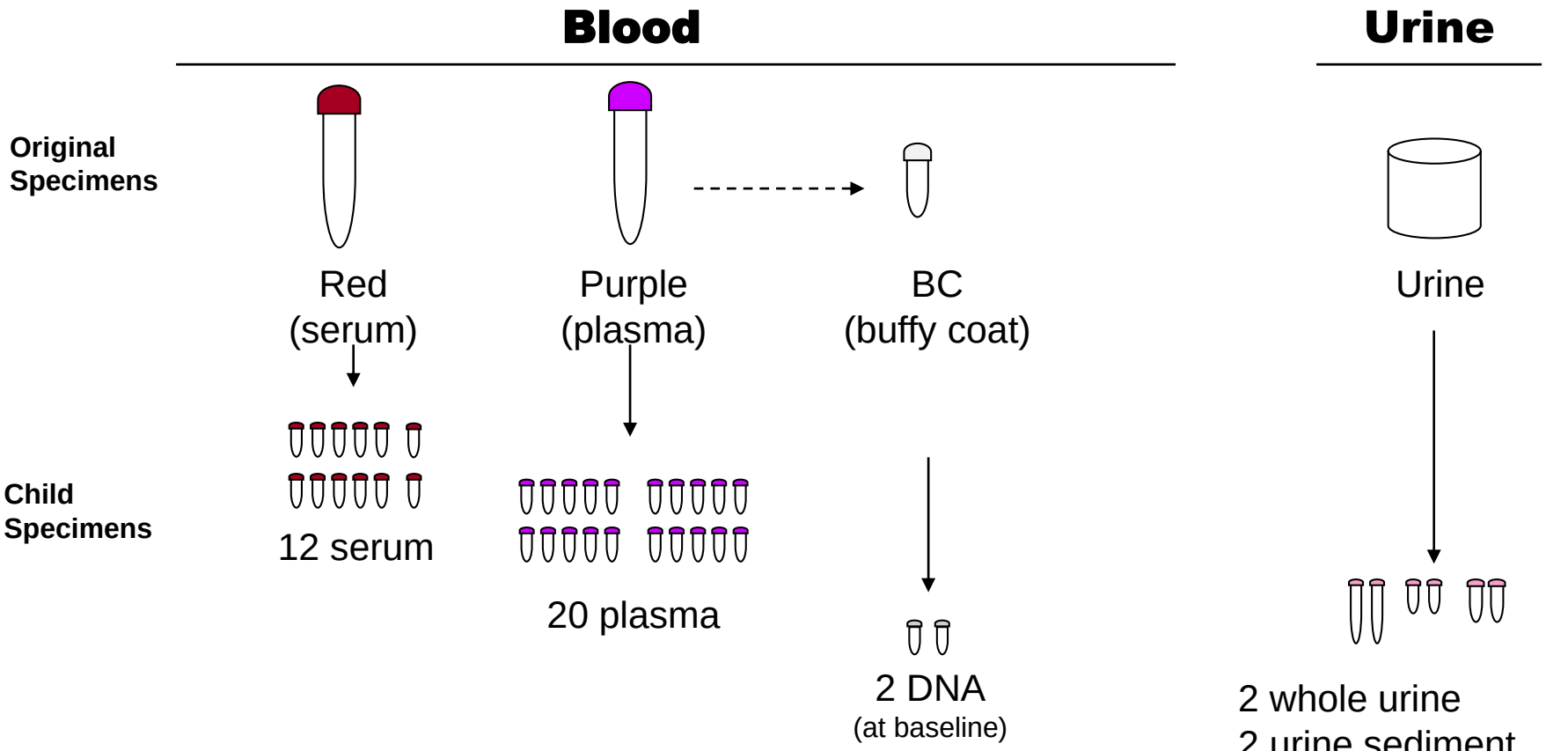
PAST:

- Strategy to avoid overtreatment of clinically indolent disease
  - Goals: reduce morbidity and side effects of radical primary treatment, increase acceptability of surveillance

PRESENT

- Strategy to identify potentially virulent disease in background of apparent indolent disease
  - Goal: refine surveillance protocols, improve triggers for intervention, *discover and validate biomarkers and predictive models*, and avoid undertreatment

Biospecimen Resource: PASS Specimens



> 340,000 specimens available for research

- At time of biopsy or RP: FFPE and frozen prostate tissue

PASS Data Elements

Collected at study entry and every 6 months, as applicable

- Demographics (age, race, BMI, family history, smoking, etc)
- Clinical (PSA, DRE, MRI, etc)
- Biopsy pathology (5 yr history)
- Medication use (statins, diabetes, hormones, NSAIDS)
- Diet (MSEL FFQ; baseline)
- Supplement Use (from SELECT; baseline and 1 year)
- HRQOL (SF-12, IPSS, EPIC26, 3-item anxiety)
- Physical activity

Collected during follow-up, if applicable

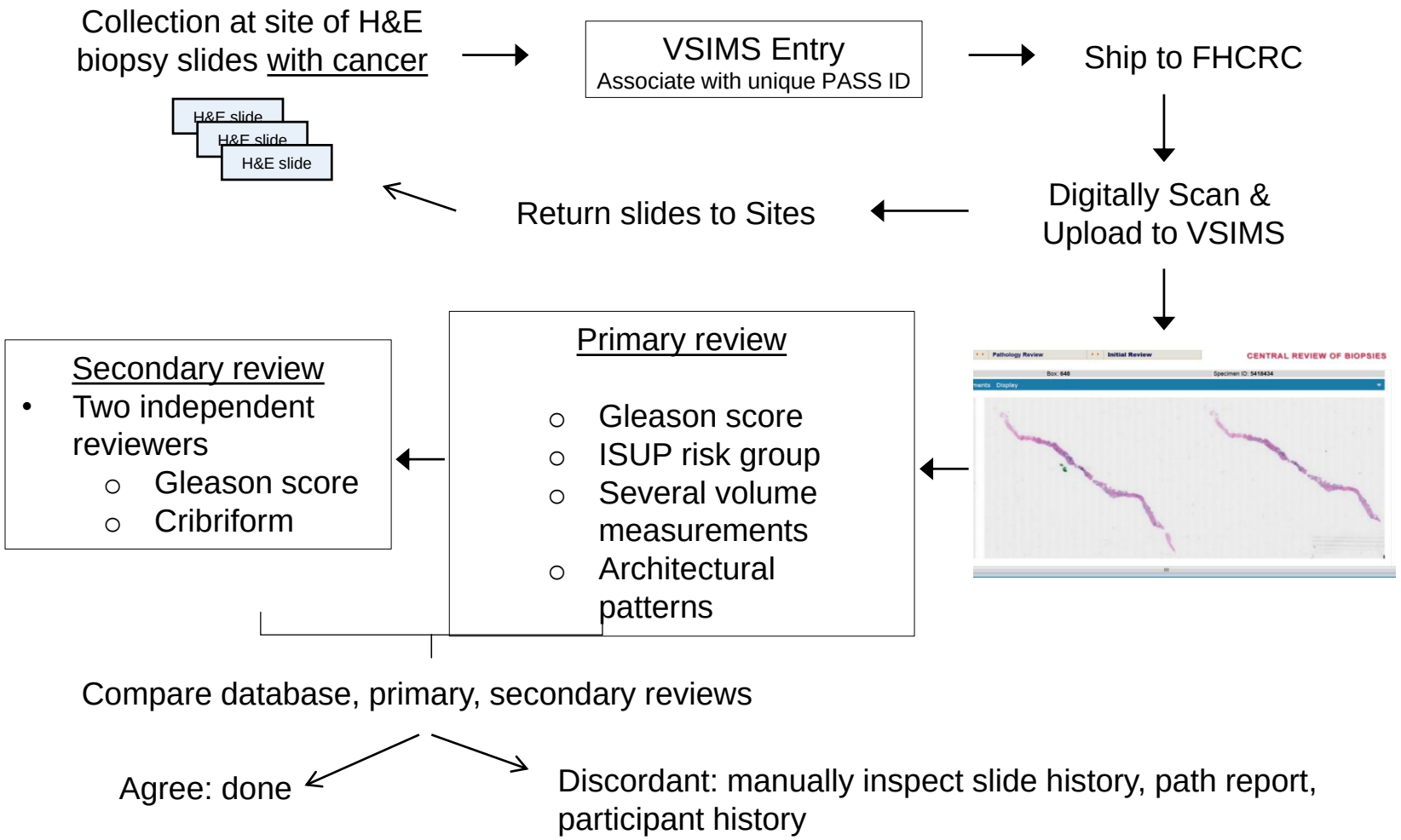
- Treatment modality
- Pathology at time of prostatectomy

Long term follow-up:

- Vital status, treatments, PSA, evidence of metastasis, death

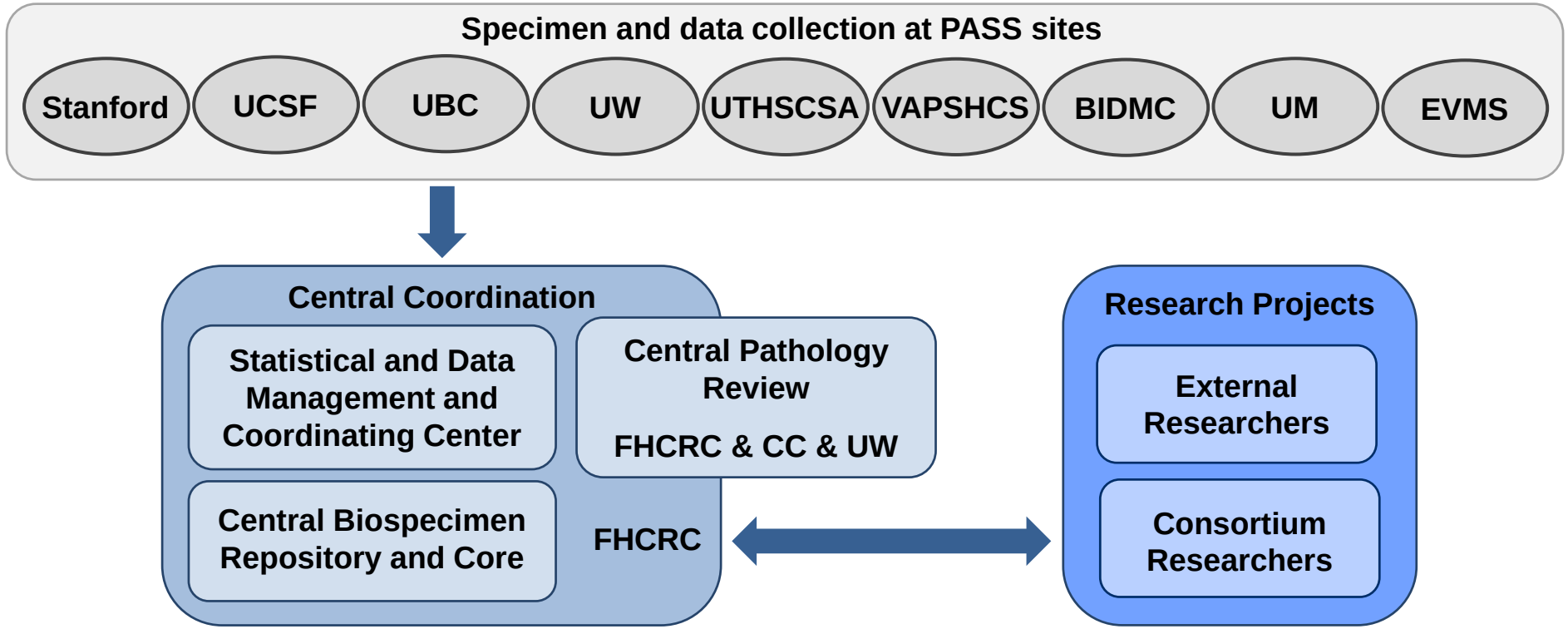
Biopsy central review performed from images

current N = 2,020 biopsies; in process



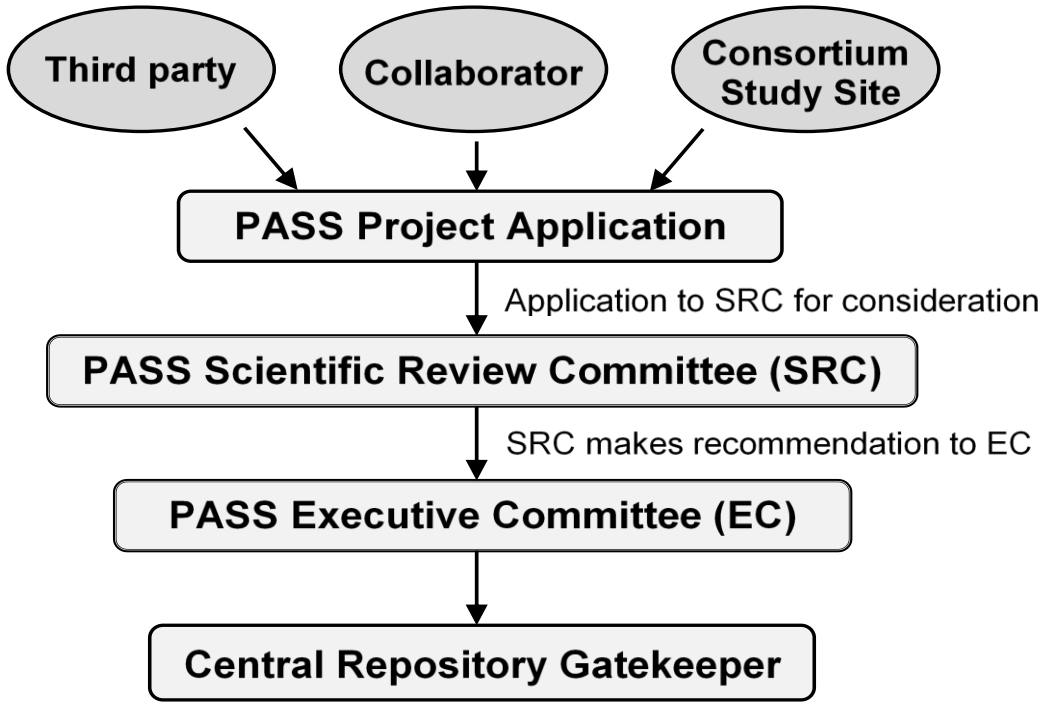
➢ RP central review performed from slides

PASS Workflow



Established procedures for collaboration

- Collaboration agreement is executed at all individual participating sites
- Fred Hutch (coordinating center) manages agreements



PASS Summary Demographics

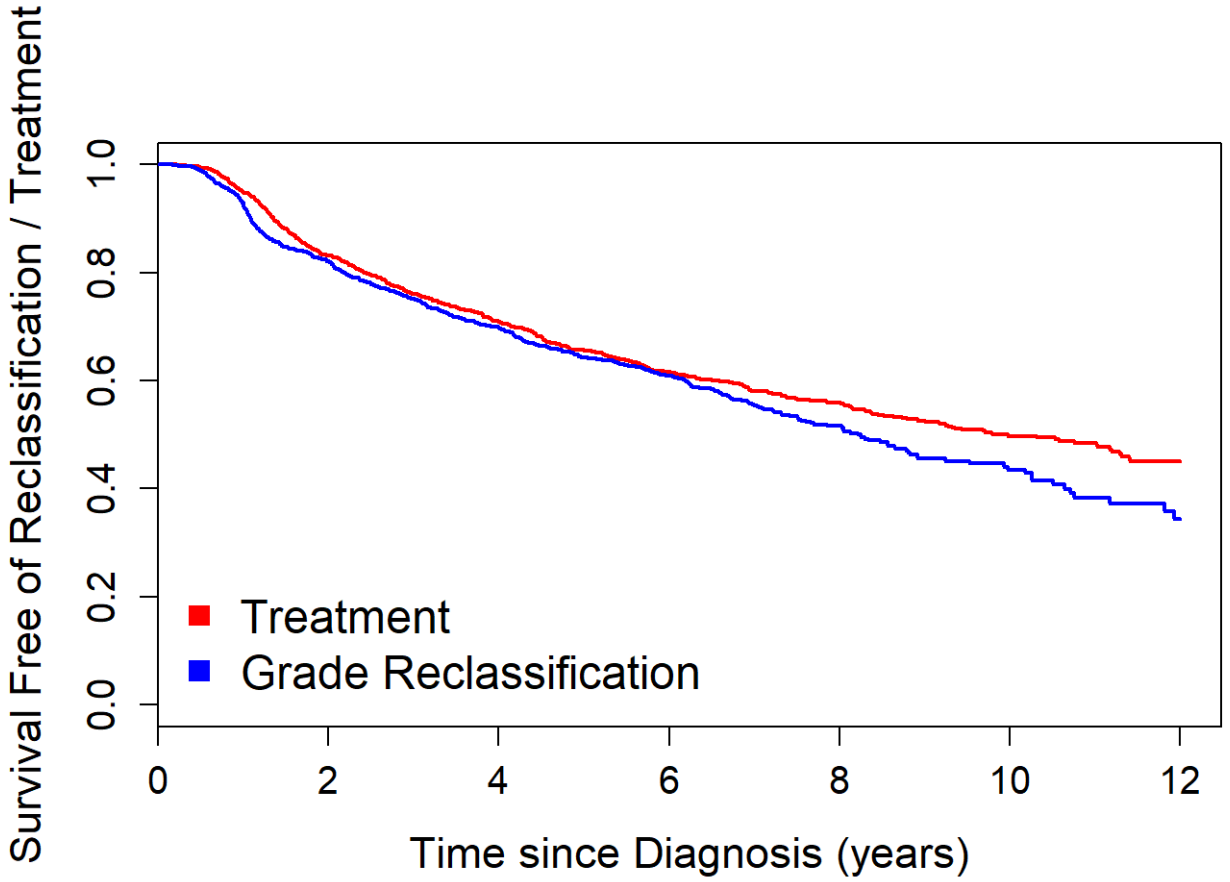
(03/24/2020, N = 2001)

- Age: median 63 years (IQR 58-67)
- Race
  - Caucasian 88%
  - African American 7%
  - Other 5%
- PSA: median 5.1 ng/mL (IQR 4.0-6.7)
- Gleason Grade Group 1: 90%

- Prostate size: median 44 cm^3 (IQR 32-58)
  - PSA Density: median 0.11 (IQR 0.08 – 0.16)
- Clinical T-stage: 88% T1c
- Tumor volume (% cores with cancer): median 12% (IQR 8.3-16.7)

Reclassification and Treatment while on AS

(03/24/20, N =2001)



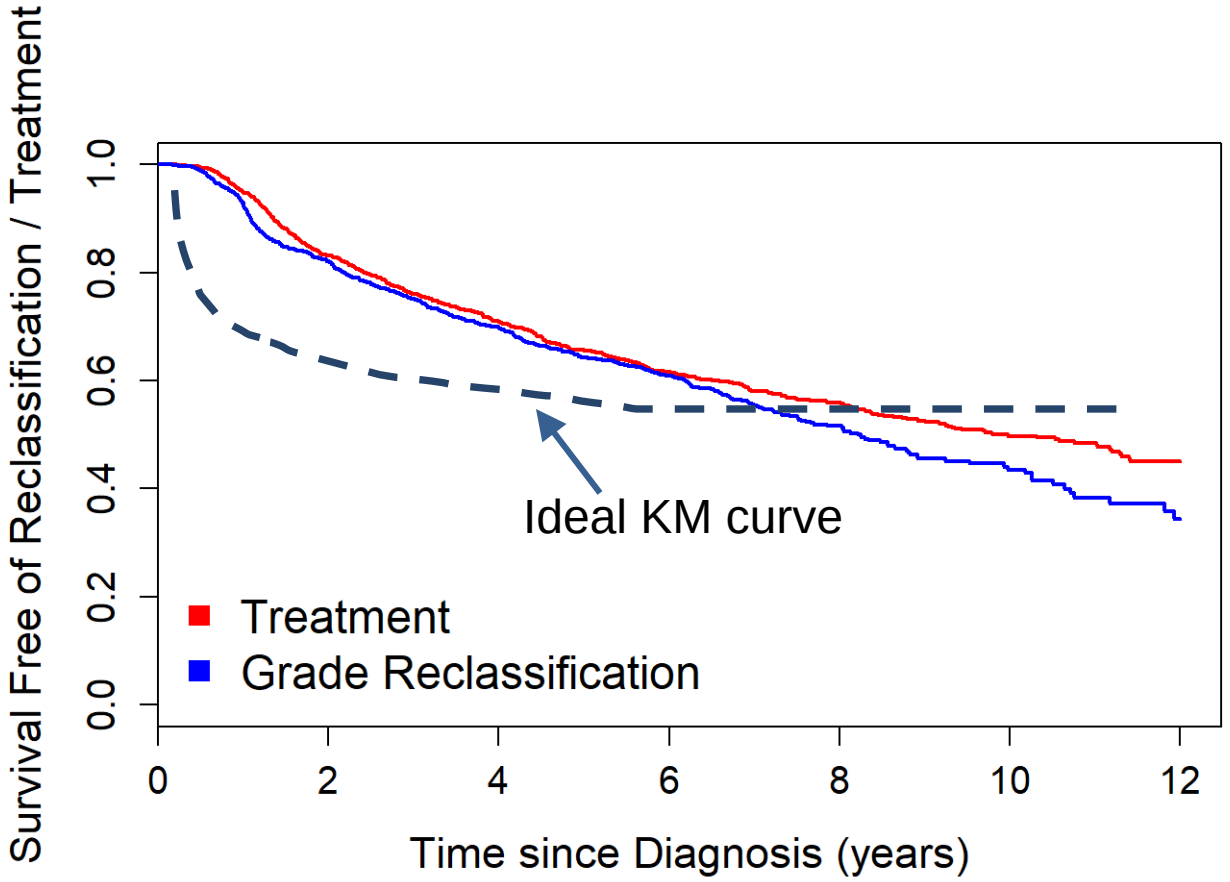
Median Survival Time:

Treatment: 10 Years
Grade-only: 8.3 Years

Outcome	Number at Risk						
	0	2	4	6	8	10	12
Grade Reclass.	2001	1309	735	431	202	75	23
Treatment	2001	1408	927	655	415	198	74

Reclassification and Treatment

(03/24/20, N =2001)



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Outcome	Number at Risk						
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Grade Reclass.	2001	1309	735	431	202	75	23
Treatment	2001	1408	927	655	415	198	74

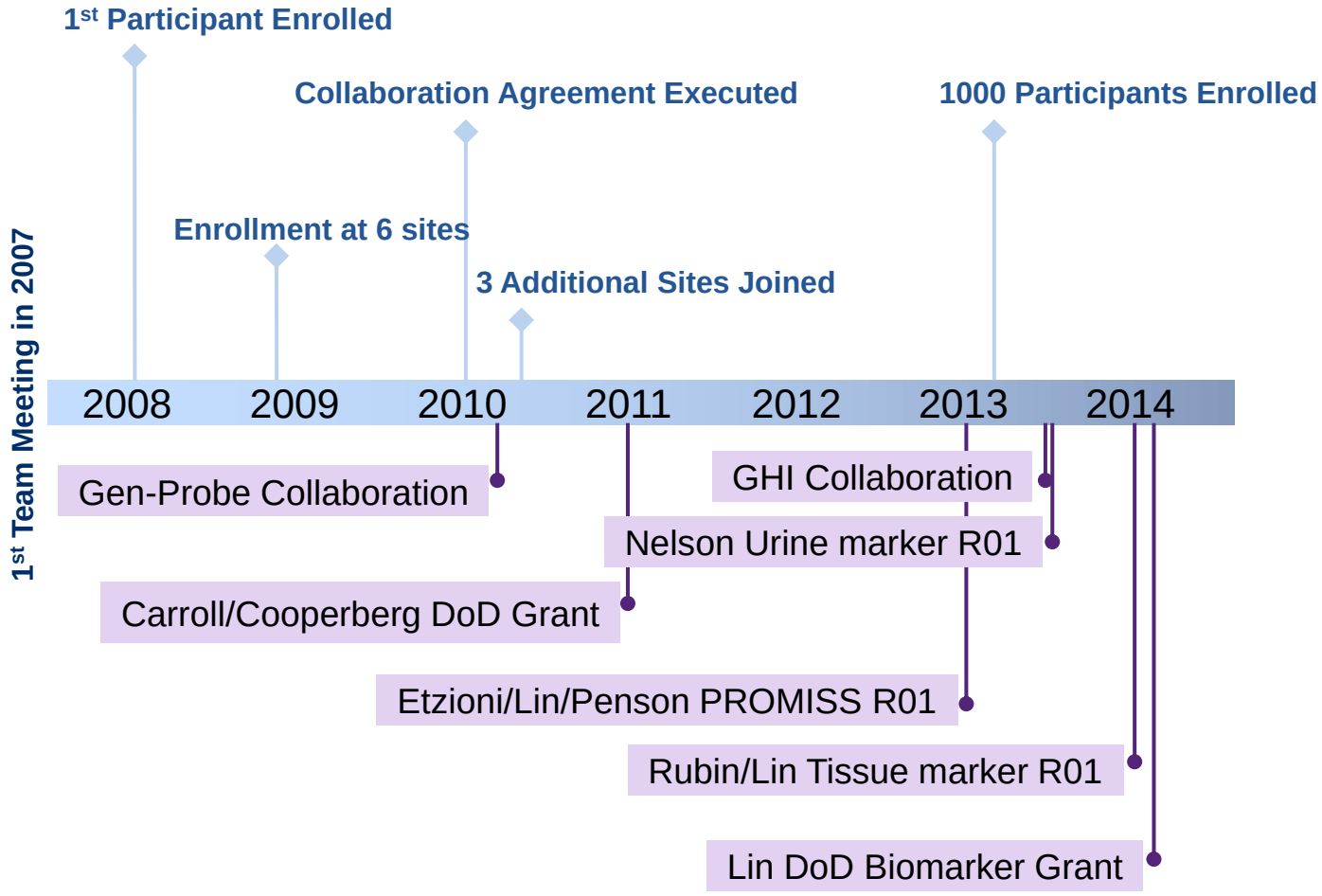
PASS Outcomes

- Follow-up (dx to last contact) Median = 5.8 yr (IQR: 2.6-8.7 yr)

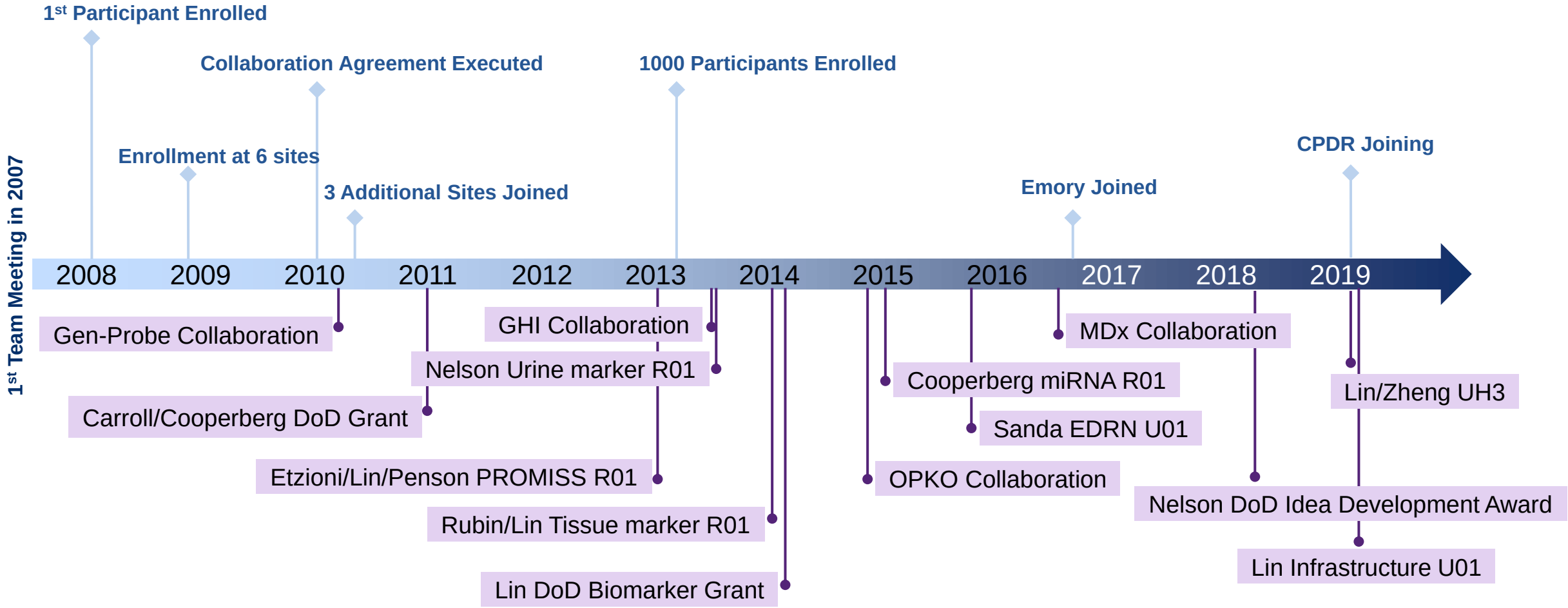
<u>Outcomes</u>

- Biopsy Grade Reclassification: 655 (33% of cohort)
- Treatment: 707 (35% of cohort) – 403 surgery and 268 radiation
  - Adverse path at surgery (≥ GG3, ≥ pT3a, or N1): 179 (44%)
  - Adverse path at surgery (≥ GG3, ≥ pT3b, or N1): 121 (30%)
  - Recurrence: 55 (median follow-up after treatment: 3.3 years)
- Survival
  - Distant Metastatic Disease: 11
  - Death due to prostate cancer: 0 (pending review)
  - Death due to other causes: 52

Canary PASS Grants and Collaborations



Canary PASS Grants and Collaborations



Biomarkers in PASS: improved risk stratification

<u>Biomarkers under investigation in PASS</u>

- Blood:
  - 4Kscore (commercially available test)
  - PSA kinetics
  - PHI (commercially available test)
  - miRNA
  - Germline DNA mutations
- Urine:
  - PCA3 (commercially available test)
  - TMPRSS2/ERG fusion protein (commercially available test)
  - Select MDx (commercially available test)
- Tissue:
  - Oncotype Dx GPS™ (commercially available test)
  - NGS

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European Association of Urology

Prostate Cancer

Evaluating the Four Kallikrein Panel of the 4Kscore for Prediction of High-grade Prostate Cancer in Men in the Canary Prostate Active Surveillance Study

Daniel W. Lin [a,b,c,*], *Lisa F. Newcomb* [a,b], *Marshall D. Brown* [a], *Daniel D. Sjoberg* [d], *Yan Dong* [e], *James D. Brooks* [f], *Peter R. Carroll* [g], *Matthew Cooperberg* [g], *Atreya Dash* [c], *William J. Ellis* [b], *Michael Fabrizio* [h], *Martin E. Gleave* [i], *Todd M. Morgan* [j], *Peter S. Nelson* [a], *Ian M. Thompson* [k], *Andrew A. Wagner* [l], *Yingye Zheng* [a],

for the Canary Prostate Active Surveillance Study Investigators

Lin et al, Eur Urol 2017; 72:448-45

Candidate Predictors

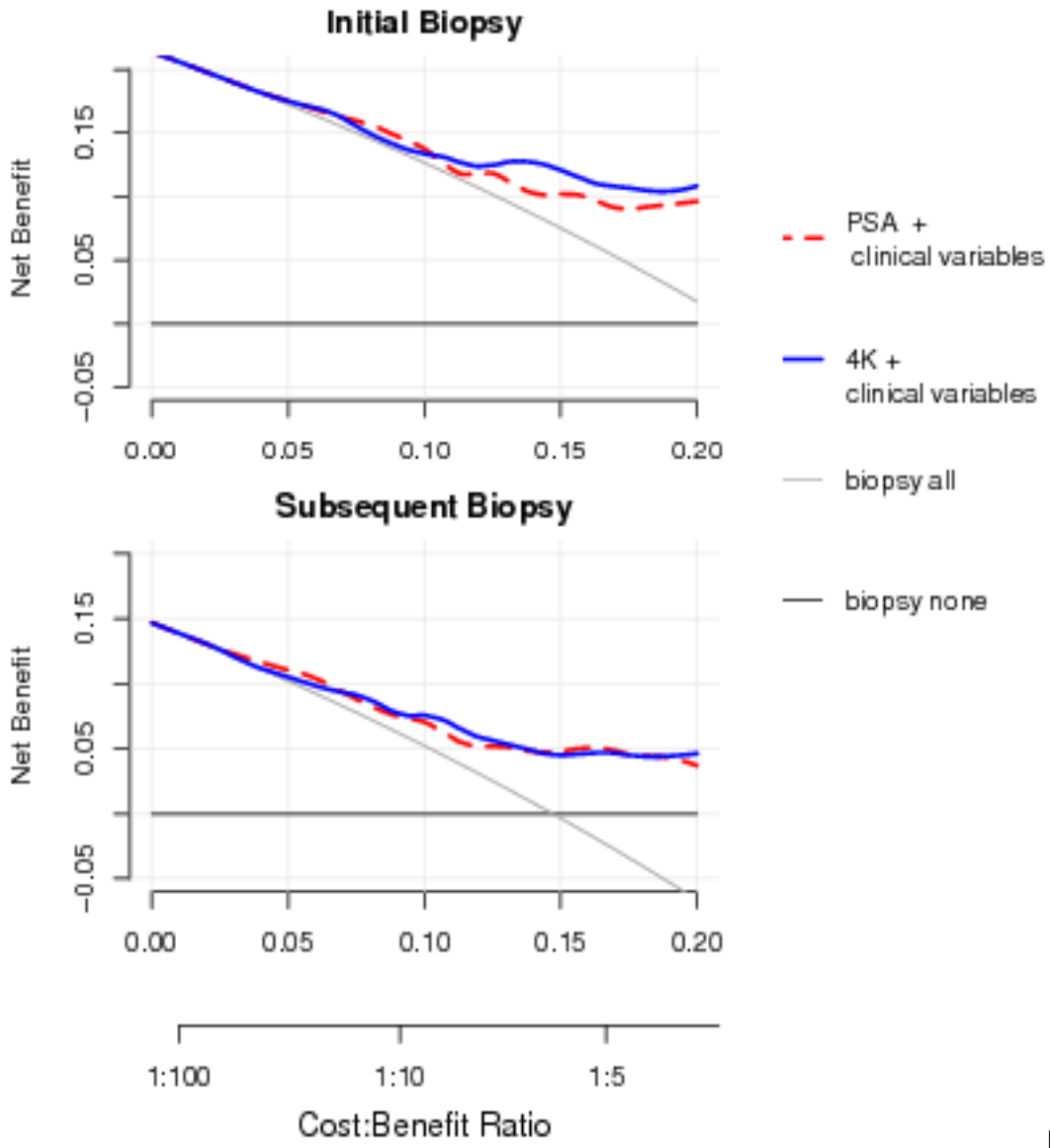
- Age
- BMI
- African American
- DRE (imputed with cT-stage)
- Number of previous biopsies (categorical; 2, 3, 4, 5…)
- Number of previous negative biopsies (categorical; 1, 2, ≥3)
- Positive cores ratio (positive cores/total cores) from previous biopsy
- Maximum of positive cores ratio of all previous biopsies
- Months between dx and biopsy
- Prostate volume: Prostate size closest to sampling (imputed w/in 2-yr interval), log scale
- 4K panel: score with OPKO combination of fPSA, tPSA, iPSA, hK2, and age. logit scale
- Clinical serum PSA value (in models without 4K), log scale
- PSA Density:
  - models with kallikreins: OPKO tPSA used
  - models with no kallikreins: Serum PSA from clinic used
- PSA velocity

Summary of Fitted Models

Variable	PSA + Clinical Model			4K + Clinical Model		
	OR	CI	p-value	OR	CI	p-value
Age	1.03	(1.00,1.06)	0.068			
BMI	1.11	(1.06,1.16)	<0.001	1.09	(1.04,1.14)	<0.001
Cores Ratio >0.2	2.19	(1.39,3.44)	0.001	2.1	(1.33,3.32)	0.001
Negative Biopsies ≥2	0.19	(0.04,0.80)	0.023	0.19	(0.04,0.85)	0.029
Log(Prostate Volume)	0.31	(0.20,0.48)	<0.001	0.47	(0.31,0.70)	<0.001
Log(PSA)	2.11	(1.53,2.91)	<0.001			
4K panel				1.54	(1.31,1.81)	<0.001

Lin et al, Eur Urol 2017

Decision Curve Analysis



Lin et al, Eur Urol 2017

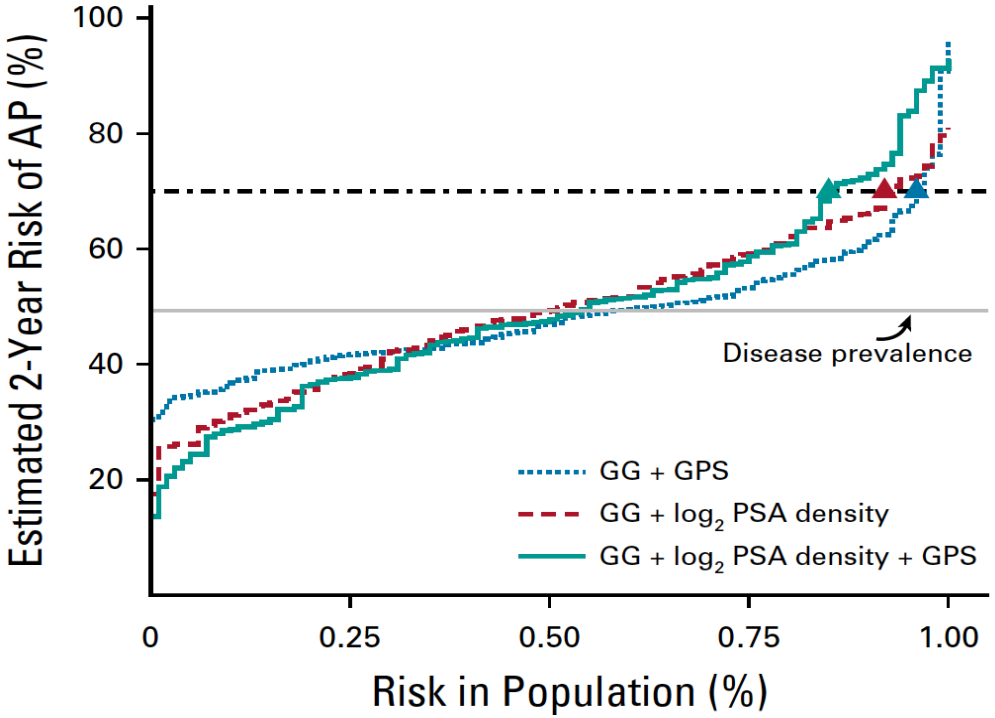
original reports

17-Gene Genomic Prostate Score Test Results in the Canary Prostate Active Surveillance Study (PASS) Cohort

Daniel W. Lin, MD[1,2]; Yingye Zheng, PhD[3]; Jesse K. McKenney, MD[4]; Marshall D. Brown, MS[3]; Ruixiao Lu, PhD[5]; Michael Crager, PhD[5]; Hilary Boyer, BS[1,2]; Maria Tretiakova, MD, PhD[6]; James D. Brooks, MD[7]; Atreya Dash, MD[8]; Michael D. Fabrizio, MD[9]; Martin E. Gleave, MD[10]; Suzanne Kolb, MPH[1]; Michael Liss, MD[11]; Todd M. Morgan, MD[12]; Ian M. Thompson, MD[13]; Andrew A. Wagner, MD[14]; Athanasios Tsiatis, MD[15]; Andrea Pingitore, MD[5]; Peter S. Nelson, MD[16]; and Lisa F. Newcomb, PhD[1,2]

TABLE 3. Multivariable Models for Adverse Pathology (n = 101)

Variable	HR[a] (95% CI)	*P*
Model 1		
GPS (per 5 units)	1.18 (1.04 to 1.44)	.030
Gleason GG 2 *v* 1	0.62 (0.24 to 1.33)	.26
Model 2		
GPS (per 5 units)	1.17 (1.00 to 1.43)	.066
Gleason GG 2 *v* 1	0.61 (0.24 to 1.24)	.24
Log_2 PSA density	1.75 (1.11 to 3.21)	.025



Lin et al, JCO 2020

Canary PASS MRI Experience

		Gleason Grade Group						Total
		No Cancer	1	2	3	4	5	
PIRADS Score	1	17	22	6	1	0	0	**46**
	2	12	11	6	1	1	0	**31**
	3	22	26	13	0	0	1	**62**
	4	16	58	21	8	3	2	**108**
	5	4	12	10	5	2	0	**33**
Total		**71**	**129**	**56**	**15**	**6**	**3**	**280**

NPV = 80%

PPV = 32%

Liss et al, J Urol, in press 2020

PASS Model with MRI for Gleason Upgrading

	Clinical Model	
	OR (95% CI)	p-value
Age	1.08 (1.03-1.14)	0.001
BMI	1.05 (0.98-1.14)	0.164
Ratio positive/total cores	1.02 (0.99-1.04)	0.156
Log(Prostate size)	0.17 (0.07-0.38)	<0.001
Log(PSA)	2.06 (1.33-3.29)	0.002
≥2 Prior Neg Biopsy	0.42 (0.13-1.18)	0.123

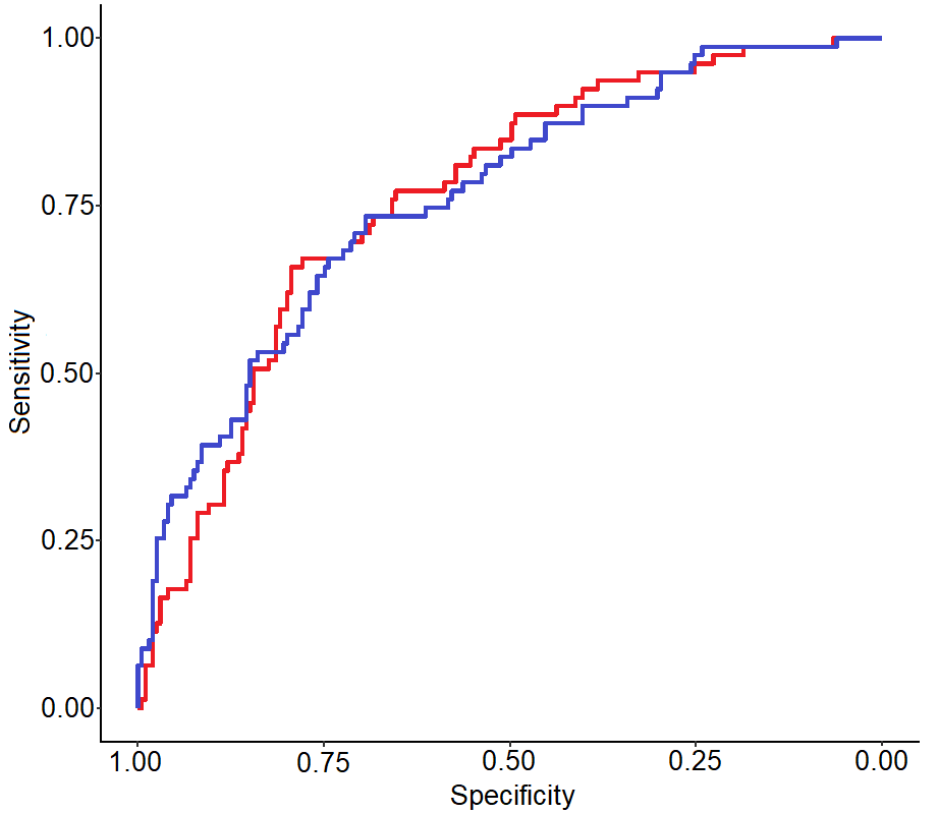
Liss et al, J Urol, in press 2020

PASS Model with MRI for Gleason Upgrading

		Clinical Model		Clinical + MRI Model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age		1.08 (1.03-1.14)	0.001	1.09 (1.04-1.14)	0.001
BMI		1.05 (0.98-1.14)	0.164	1.05 (0.98-1.14)	0.180
Ratio positive/total cores		1.02 (0.99-1.04)	0.156	1.01 (0.99-1.04)	0.305
Log(Prostate size)		0.17 (0.07-0.38)	<0.001	0.18 (0.07-0.39)	<0.001
Log(PSA)		2.06 (1.33-3.29)	0.002	1.95 (1.24-3.16)	0.005
≥2 Prior Neg Biopsy		0.42 (0.13-1.18)	0.123	0.37 (0.11-1.05)	0.080
PIRADS (1-2 reference)	3			0.84 (0.33-2.06)	0.698
	4			1.19 (0.56-2.58)	0.663
	5			3.22 (1.20-8.87)	0.021

Liss et al, J Urol, in press 2020

ROC Analysis for Prediction of Upgrading



Liss et al, J Urol, in press 2020

Refined Analysis of Prostate-specific Antigen Kinetics to Predict Prostate Cancer Active Surveillance Outcomes

Matthew R. Cooperberg [a,b,], James D. Brooks [c], Anna V. Faino [d], Lisa F. Newcomb [e,f], James T. Kearns [f], Peter R. Carroll [a], Atreya Dash [f], Ruth Etzioni [d], Michael D. Fabrizio [g], Martin E. Gleave [h], Todd M. Morgan [i], Peter S. Nelson [j], Ian M. Thompson [k], Andrew A. Wagner [l], Daniel W. Lin [e,f], Yingye Zheng [d]*

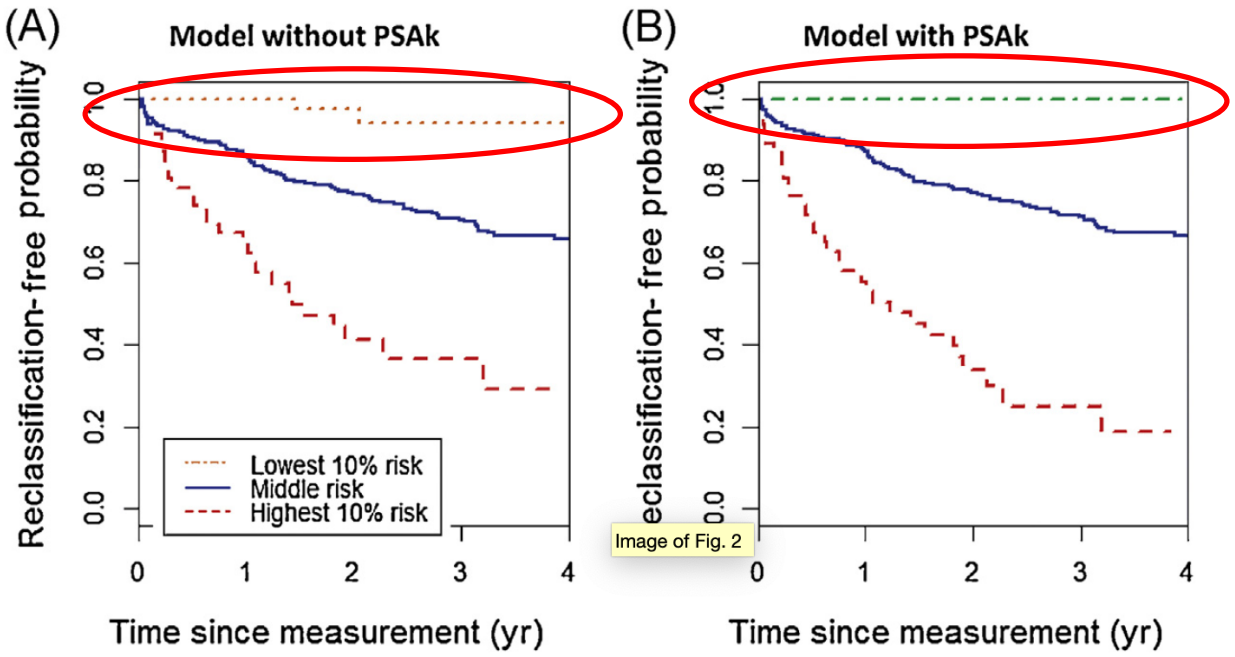


Image of Fig. 2

Model-based risk group [a]	Reclassification-free probability at 4 yr after the 1-yr measurement time (95% CI)	
	Model without PSAk	Model with PSAk
Lowest 10% risk	0.94 (0.87, 1.00)	1.00 (1.00, 1.00)
Middle risk	0.66 (0.60, 0.72)	0.66 (0.61, 0.72)
Highest 10% risk	0.41 (0.28, 0.60) [b]	0.34 (0.22, 0.53) [b]

Cooperberg et al, Eur Urol 2018

When active surveillance can be less active: tailoring intensity of monitoring based on prediction of non-reclassification for men with low-risk prostate cancer

Cooperberg et al, JAMA Onc, in press 2020

Matthew R. Cooperberg, Yingye Zheng, Anna V. Faino, Lisa F. Newcomb, Kehao Zhu, Janet E. Cowen, James D. Brooks, Frances Martin, Martin E. Gleave, Todd M. Morgan, Atreya Dash, Peter S. Nelson, Ian M. Thompson, Andrew A. Wagner, Peter R. Carroll, Daniel W. Lin

Variable	Hazard Ratio (95% CI)	P-value
Max cores ratio (10% increase)	1.29 (1.08, 1.55)	0.005
Prior Negative Biopsy		
1 vs 0	0.51 (0.37, 0.70)	<.001
2+ vs 0	0.17 (0.08, 0.38)	<.001
Ln time since diagnosis (yrs)	2.22 (1.52, 3.24)	<.001
BMI	1.09 (1.05, 1.12)	<.001
Ln prostate size (cc)	0.39 (0.25, 0.62)	<.001
Ln diagnostic PSA	1.52 (1.16, 2.00)	0.003
PSAk (0.10 increase)	1.45 (1.22, 1.73)	<.001

When active surveillance can be less active: tailoring intensity of monitoring based on prediction of non-reclassification for men with low-risk prostate cancer

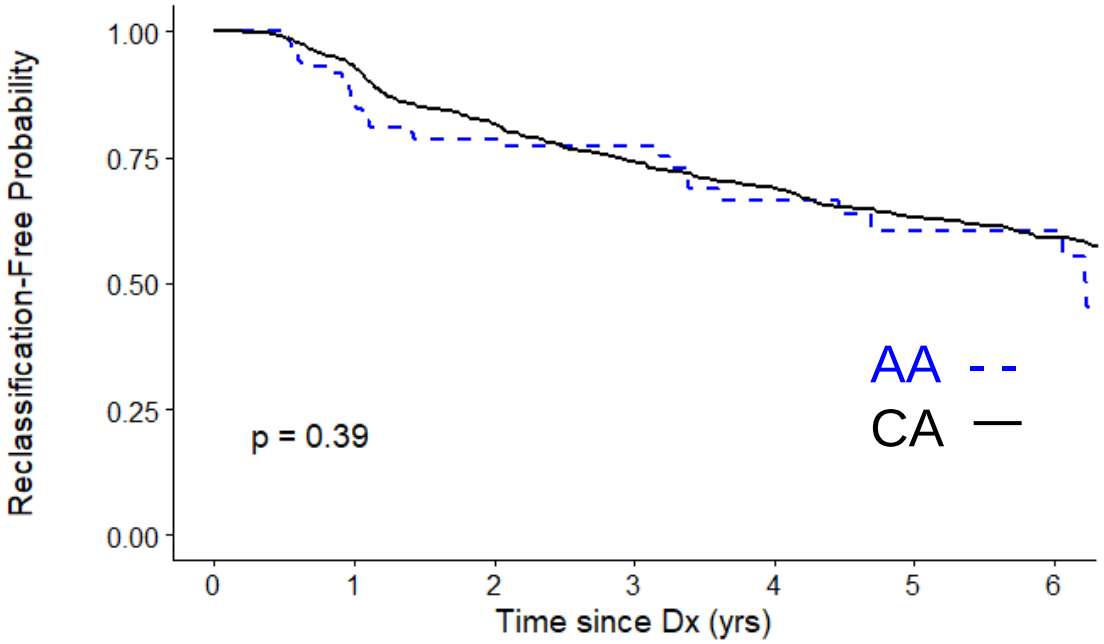
Cooperberg et al, JAMA Onc, in press 2020

Matthew R. Cooperberg, Yingye Zheng, Anna V. Faino, Lisa F. Newcomb, Kehao Zhu, Janet E. Cowen, James D. Brooks, Frances Martin, Martin E. Gleave, Todd M. Morgan, Atreya Dash, Peter S. Nelson, Ian M. Thompson, Andrew A. Wagner, Peter R. Carroll, Daniel W. Lin

Risk Threshold (Percentile)*	TPR (95% CI)~	FPR (95% CI)~	NPV (95% CI)~	PPV (95% CI)~	Follow up Avoided per 1000 men	Reclass Missed (95% CI) per 1000 men
PASS						
0.08 (10th)	0.97 (0.95, 1.00)	0.87 (0.83, 0.91)	0.94 (0.87, 1.01)	0.27 (0.23, 0.31)	100	6 (-1, 13)
0.10 (15th)	0.94 (0.89, 0.98)	0.81 (0.77, 0.85)	0.90 (0.83, 0.97)	0.27 (0.23, 0.31)	150	15 (5, 25)
0.11 (20th)	0.90 (0.85, 0.96)	0.76 (0.70, 0.79)	0.88 (0.82, 0.95)	0.28 (0.24, 0.33)	200	24 (10, 37)
0.13 (25th)	0.87 (0.82, 0.94)	0.69 (0.63, 0.73)	0.88 (0.83, 0.94)	0.29 (0.25, 0.34)	250	30 (13, 43)

African American Race is Not Associated with Risk of Reclassification during Active Surveillance: Results from the Canary Prostate Cancer Active Surveillance Study

Jeannette M. Schenk,* Lisa F. Newcomb, Yingye Zheng, Anna V. Faino, Kehao Zhu, Yaw A. Nyame, James D. Brooks, Peter R. Carroll, Matthew R. Cooperberg, Atreya Dash, Christopher P. Filson, Martin E. Gleave, Michael Liss, Francis M. Martin, Todd M. Morgan,† Peter S. Nelson, Ian M. Thompson, Andrew A. Wagner and Daniel W. Lin



	Multivariable	
	HR (95% CI)^	p-value^
AA race	1.16 (0.78 – 1.72)	0.46
Age	1.03 (1.01 – 1.04)	<0.001
Gleason GG	0.66 (0.44 – 0.97)	0.04
% positive cores	1.34 (1.24 – 1.45)	<0.001
Prostate size	0.40 (0.32 – 0.50)	<0.001
PSA	1.67 (1.41 – 1.97)	<0.001
BMI	1.05 (1.02 – 1.07)	0.001
Family history	0.96 (0.77 – 1.19)	0.71

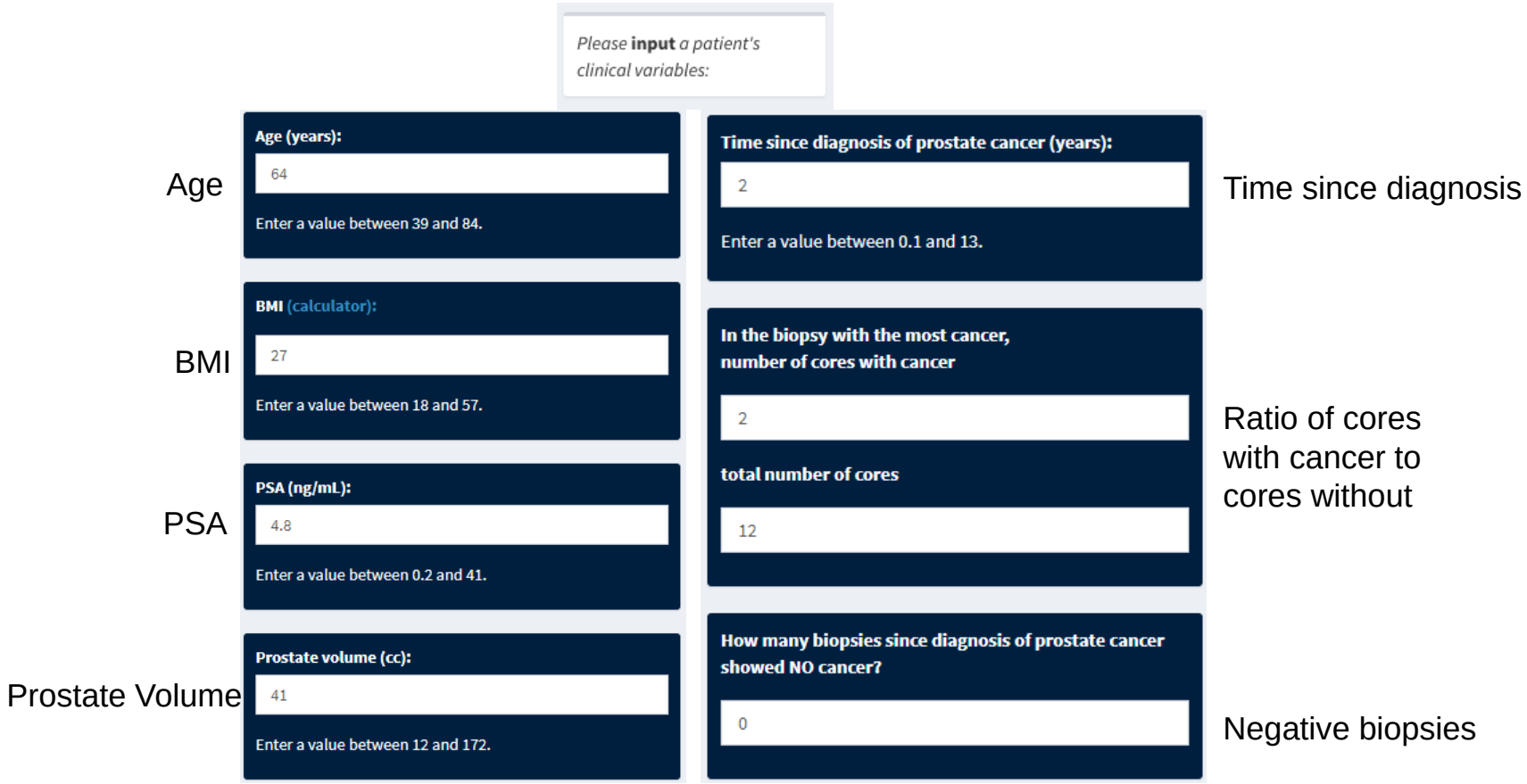
Schenk et al, J Urol 2020

Canary PASS Risk Calculator 1.0

https://canarypass.org/calculators/

Ankerst et al, Eur Urol. 2015

Canary PASS Risk Calculator Interface



Canary PASS Risk Calculator Interface

Please **input** *a patient's clinical variables:*

Age (years):
60
Enter a value between 39 and 84.

BMI (calculator):
29
Enter a value between 18 and 57.

PSA (ng/mL):
5.7
Enter a value between 0.2 and 41.

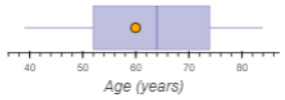
Prostate volume (cc):
46
Enter a value between 12 and 172.

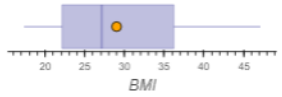
Time since diagnosis of prostate cancer (years):
1
Enter a value between 0.1 and 13.

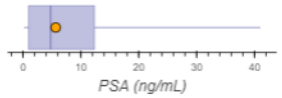
In the biopsy with the most cancer, number of cores with cancer
2
total number of cores
12

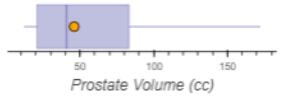
How many biopsies since diagnosis of prostate cancer showed NO cancer?
0

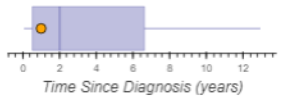
The shaded box **shows the interquartile range** *of the clinical variable, and the lines extend to the 5th and 95th percentiles. The orange point shows the* **patient's value** *as input in the left column.*

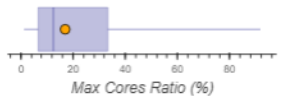










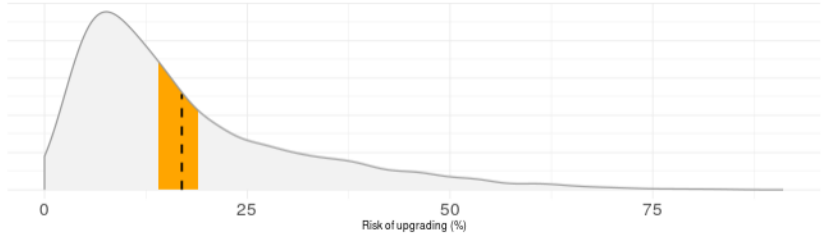


The figure below shows the distribution of risk in the PASS cohort. The black vertical line shows the **estimated personalized risk** *for the patient upgrading at the next biopsy. The bands around the point show 95% confidence intervals for the estimated risk.*

Risk of Gleason upgrade at next biopsy:

17%

95% confidence interval: (14% - 19%)



How does the estimated risk rank among the AS population?

63%

of the AS population have lower risk.

PASS: Prostate Active Surveillance Study

Ongoing, planned, or potential projects

- Germline/epigenomic studies (Catalona, Northwestern SPORE)
- Tumor sequencing (Rubin/Mosquera R01)
- HRQOL/PRO
  - Drivers of decision-making
  - Treatment in the absence of clinical progression
- Costs effectiveness research in AS strategies
  - Multiple sources of costs: serial biopsy, imaging, genomic testing
  - Impact of delayed treatment
- Dissemination and Implementation of risk tools
- Lifestyle/diet/physical activity data available

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Jonathan Wright

VA Puget Sound
Atreya Dash

Industrial collaborations
GHI
OPKO
Hologic/Gen-Probe
MDx Health

Patient advocate
Merel Grey

- Numerous study coordinators, clinicians, research personnel, and **all PASS participants**

Support
Canary Foundation (Heidi Auman, Sarah Hawley, Don Listwin)
Early Detection Research Network/NCI, NIH, Institute for Prostate Cancer Research, DoD

PASS: Prostate Active Surveillance Study

Clinical Sites: BIDMC • Emory • EVMS • Stanford • UBC • UCSF • U Michigan • UTHSCSA • UW • VAPSHCS **Coordinating Center:** FHCRC