APPENDIX A. GENOMIC CLASSIFIER GUIDELINE TABLES

Organization	Clinical Context in Which Test Is Recommended (*eg*, Patient Characteristics, Role in Decision Making)	Citation

ASCO	• **Active surveillance, prostate cancer**
	  • "Commercially available molecular biomarkers (*ie*, Oncotype Dx Prostate, Prolaris, Decipher, and Promark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence Based; Evidence quality: Insufficient; Strength of recommendation: Moderate)"
	• **Diagnosis of clinically significant prostate cancer**
	  • "Commercially available molecular biomarkers (*ie*, Oncotype Dx Prostate, Prolaris, Decipher, and Promark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence Based; Evidence quality: Intermediate; Strength of recommendation: Moderate)"
	• **Postprostatectomy when choosing adjuvant versus salvage radiation**
	  • "The expert panel recommends consideration of a commercially available molecular biomarker (*eg*, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence-based; Evidence quality: Intermediate; Strength of recommendation: Moderate)"
		Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline
		
		https://ascopubs.org/doi/full/10.1200/JCO.19.02768
		
		Eggener SE, Rumble RB, Armstrong AJ, Morgan TM, Crispino T, Cornford P, van der Kwast T, Grignon DJ, Rai AJ, Agarwal N, Klein EA, Den RB, Beltran H. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol. 2020 May 1;38(13):1474-1494. doi: 10.1200/JCO.19.02768. Epub 2019 Dec 12. PMID: 31829902.

AUA/ ASTRO	• "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)" • "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B) • "the Panel concluded that clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-	**Clinically Localized Prostate Cancer: AUA/ASTRO Guideline (2022)** https://www.auanet.org/guidelines/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022 Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, part I:

Organization	Clinical Context in Which Test Is Recommended (*eg*, Patient Characteristics, Role in Decision Making)	Citation
	making; however, clinicians may use such tests selectively when added risk stratification make alter shared decision making."	introduction, risk assessment, staging, and risk-based management. J Urol. 2022;208(1):10-18

NCCN	• "Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris."
	• "The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy, and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B)."
	• For Clinically Localized Disease
	  • All three relevant gene expression tests noted to be recommended for prognostic and not predictive purposes
	  • Decipher: noted to be trained for distant metastases (level of validation evidence 1)
	  • Prolaris: validated for multiple endpoints but not trained for a specific endpoint (level of validation evidence: 3)
	  • Oncotype: noted to be trained for adverse pathology (level of validation evidence 3)
		NCCN Clinical Practice Guidelines: Prostate Cancer Version 1.2023
		
		prostate.pdf (nccn.org)

ESMO	• "Tissue-based molecular assays may be used in conjunction with clinicopathological factors for treatment decision making in localised prostate cancer [IV, C]"	Prostate Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up https://www.annalsofoncology.org/article/S0923-7534(20)39898-7/fulltext#secsectitle0150

Notes. [a] Now called Genomic Prostate Score (GPS) test (MDxHealth).

Prostate Cancer Genomic Classifiers Summary

	Decipher	Genomic Prostate Score	Prolaris
Specimen type	Biopsy, radical prostatectomy	Biopsy	Biopsy, radical prostatectomy
Assay gene coverage	22 genes (7 cancer pathways)	12 prostate cancer related genes and 5 reference genes	31 CCP genes, 15 reference genes
Scoring	0-0.45 (Low), 0.45-0.60 (intermediate), and 0.60-1.0 (high) risk Range 0-1 (higher score=higher risk)	Low, intermediate, and high risk Range 0-100 (higher score=higher risk)	Majority of scores from 1-11 (higher score=higher risk)
Company	Veracyte	MDxHealth	Myriad Genetics

APPENDIX B. SEARCH STRATEGIES

Database: MEDLINE (via Ovid)
Search date: 4/24/2022
Note: Ovid MEDLINE(R) ALL 1946 to April 22, 2022

Search Set	Search Strategy	Results
#1	exp Prostatic Neoplasms/ OR ((prostate OR prostatic) ADJ5 (cancer OR cancers OR cancerous OR neoplasm OR neoplasms OR neoplasia OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas OR malignancy OR malignancies OR tumor OR tumors OR tumour OR tumours)).ti,ab,kw,kf.	189,179
#2	(decipher OR prolar?s OR "oncotype Dx" OR OncotypeDx OR GPS).ti,ab,kw,kf.	41,034
#3	((genomic OR genomics OR CCP OR cycle cell proliferat* OR cycle cell progression*) ADJ4 (test OR tests OR testing OR biomarker OR biomarkers OR bio-marker OR bio-markers OR marker OR markers OR classifier OR classifiers OR score OR scores OR scoring OR assay OR assays)).ti,ab,kw,kf.	10,079
#4	((tissue-based OR "tissue based" OR tissue?based) ADJ4 (biomarker OR biomarkers OR bio-marker OR bio-markers OR marker OR markers OR classifier OR classifiers OR score OR scores OR scoring OR assay OR assays)).ti,ab,kw,kf.	412
#5	exp Biomarkers, Tumor/ AND exp Genomics/	5,741
#6	2 or 3 or 4 or 5	56,616
#7	1 and 6	1,213
#8	Limit 7 to da=20100101-20221231	1,013
#9	8 not (exp animals/ not exp humans/)	1,008
#10	9 not (case reports OR editorial OR letter OR comment OR congress).pt.	954

Database: Embase (via Elsevier)
Search date: 4/24/2022
Note: Search from the Results page

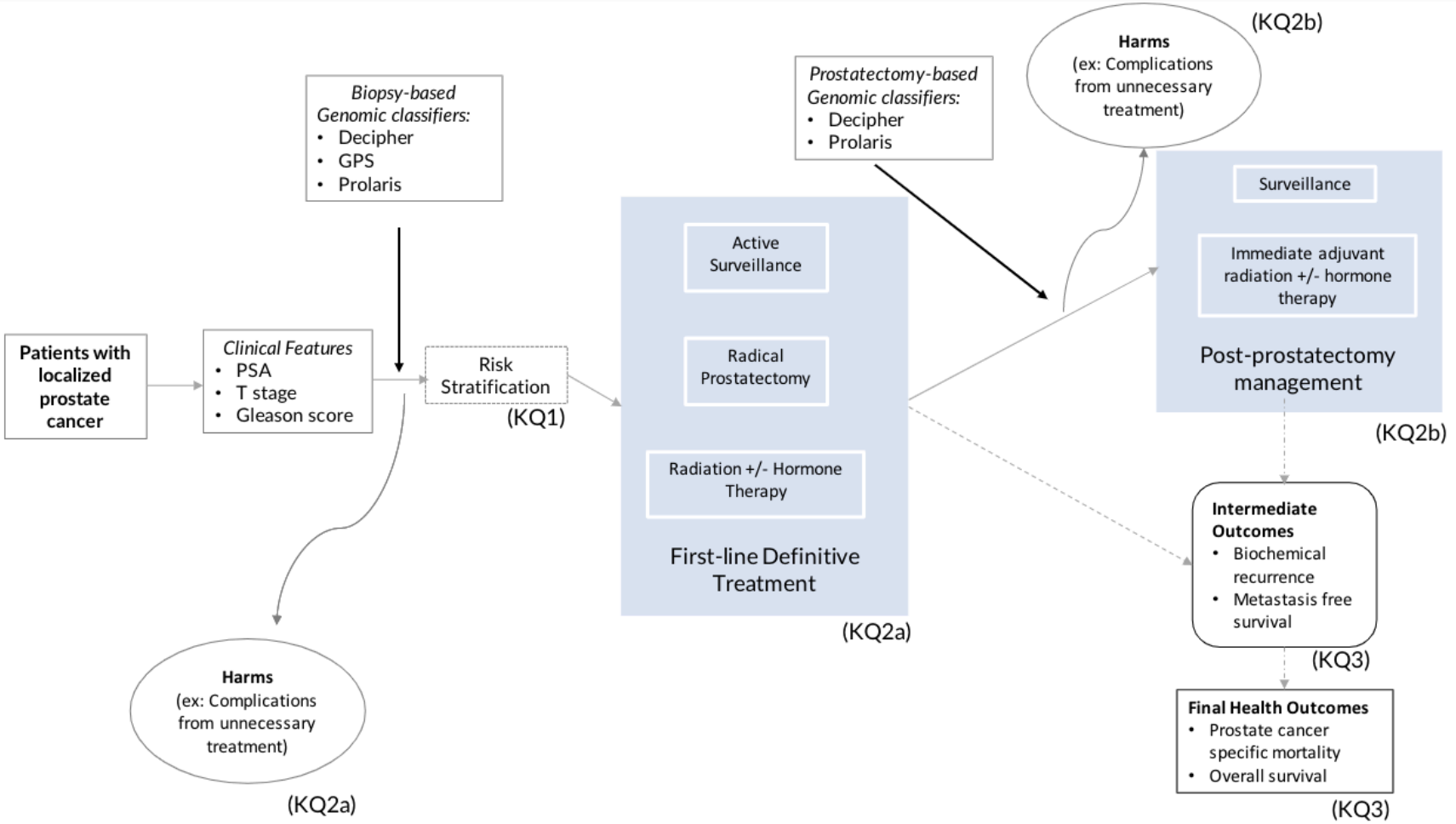
Search Set	Search Strategy	Results
#1	'prostate cancer'/exp OR ((prostate OR prostatic) NEAR/5 (cancer OR cancers OR cancerous OR neoplasm OR neoplasms OR neoplasia OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas OR malignancy OR malignancies OR tumor OR tumors OR tumour OR tumours)):ti,ab,kw	301,862
#2	(decipher OR prolar?s OR 'oncotype Dx' OR OncotypeDx OR GPS):ti,ab,kw	56,629

#3	((genomic OR genomics OR CCP OR 'cycle cell proliferation' OR 'cycle cell proliferations' OR 'cycle cell progression' OR 'cycle cell progressions') NEAR/4 (test OR tests OR testing OR biomarker OR biomarkers OR bio?marker OR bio?markers OR marker OR markers OR classifier OR classifiers OR score OR scores OR scoring OR assay OR assays)):ti,ab,kw	15,432
#4	(('tissue based' OR tissue?based) NEAR/4 (biomarker OR biomarkers OR bio?marker OR bio?markers OR marker OR markers OR classifier OR classifiers OR score OR scores OR scoring OR assay OR assays)):ti,ab,kw	880
#5	'tumor marker'/exp AND 'genomics'/exp	2,092
#6	#2 OR #3 OR #4 OR #5	74,019
#7	#1 AND #6	2,101
#8	#7 AND [01-01-2010]/sd	1,929
#9	#8 AND [humans]/lim	1,847
#10	#9 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR [editorial]/lim OR 'letter'/exp OR [letter]/lim OR 'note'/exp OR [note]/lim OR [conference abstract]/lim OR 'conference abstract'/exp OR 'conference abstract'/it)	940

Database: Web of Science (via Clarivate) – Science Citation Index Expanded (1900 – present) and Social Science Citation Index (1900 – present)
Search date: 4/24/2022
Note: Select indices under 'Editions'; use Advanced Search

Search Set	Search Strategy	Results
#1	TS=((prostate OR prostatic) NEAR/5 (cancer OR cancers OR cancerous OR neoplasm OR neoplasms OR neoplasia OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas OR malignancy OR malignancies OR tumor OR tumors OR tumour OR tumours))	243,238
#2	TS=(decipher OR prolaris OR "oncotype Dx" OR OncotypeDx OR GPS)	100,600
#3	TS=((genomic OR genomics OR CCP OR "cycle cell proliferation" OR "cycle cell proliferations" OR "cycle cell progression" OR "cycle cell progressions") NEAR/4 (test OR tests OR testing OR biomarker OR biomarkers OR bio-marker OR bio-markers OR marker OR markers OR classifier OR classifiers OR score OR scores OR scoring OR assay OR assays))	13,969
#4	TS=((tissue-based OR "tissue based") NEAR/4 (biomarker OR biomarkers OR bio-marker OR bio-markers OR marker OR markers OR classifier OR classifiers OR score OR scores OR scoring OR assay OR assays))	477
#5	#2 OR #3 OR #4	114,631
#6	#1 AND #5	1,290
#7	#7 AND (2022 or 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 or 2014 or 2013 or 2012 or 2011 or 2010 (Publication Years))	1,142
#8	#8 NOT (Meeting Abstracts or Editorial Materials or Book Chapters or Letters or News Items (Exclude – Document Types)	922

APPENDIX C. CONCEPTUAL FRAMEWORK



APPENDIX D. EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible index prognostic factor, 3=Ineligible comparator prognostic factors, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design.

Citation	
Alam, 2019[1]	4
Alshalalfa, 2017[2]	2
Alshalalfa, 2019[3]	3
Anonymous, 2018[4]	6
Arsov, 2014[5]	1
Beksac, 2018[6]	3
Beksac, 2022[7]	3
Blume-Jensen, 2015[8]	2
Brand, 2016[9]	4
Brastianos, 2020[10]	3
Canfield, 2018[11]	4
Chu, 2021[12]	4
Cooperberg, 2018[13]	2
Covas Moschovas, 2021[14]	4
Creed, 2020[15]	2
Cuzick, 2014[16]	6
Cuzick, 2021[17]	1
Den, 2014[18]	4
Den, 2016[19]	3
Ding, 2021[20]	2
Eggener, 2019[21]	4
Falagario, 2019[22]	4
Freedland, 2016[23]	1
Gaffney, 2021[24]	3
Ginsburg, 2021[25]	3
Goldberg, 2021[26]	4
Greenland, 2020[27]	4
Greenland, 2022[28]	3
Hall, 2020[29]	4
Herlemann, 2020[30]	4
Hu, 2018[31]	2
Jambor, 2020[32]	3
James, 2011[33]	1
Jhun, 2017[34]	2
Karnes, 2013[35]	1

Citation	
Kim, 2017[36]	4
Kim, 2019[37]	4
Klein, 2017[38]	4
Knudsen, 2016[39]	3
Koch, 2016[40]	1
Kornberg, 2019[41]	4
Lalonde, 2014[42]	2
Leapman, 2021[43]	3
Lee, 2016[44]	4
Lee, 2021[45]	4
Lin, 2020[46]	4
Lobo, 2015[47]	4
Lobo, 2016[48]	3
Lonergan, 2020[49]	4
Lopez, 2017[50]	4
Luca, 2020[51]	4
Magi-Galluzzi, 2018[52]	3
Mahal, 2018[53]	2
Mahal, 2020[54]	4
Marascio, 2020[55]	4
Marrone, 2015[56]	6
Martin, 2019[57]	4
Martini, 2019[58]	2
Muralidhar, 2019[59]	4
Murphy, 2020[60]	4
Nguyen, 2018[61]	2
Nyame, 2018[62]	4
Pardy, 2020[63]	3
Pellegrini, 2017[64]	2
Prensner, 2014[65]	2
Press, 2022[66]	4
Purysko, 2019[67]	3
Rai, 2019[68]	2
Ross, 2014[69]	1
Rounbehler, 2018[70]	2
Salama, 2013[71]	6
Salmasi, 2018[72]	4
Shahait, 2021[73]	5
Shoag, 2020[74]	2
Shore, 2014[75]	4

Citation	
Taylor, 2020[76]	3
Tomlins, 2015[77]	3
Torres, 2017[78]	3
Trabulsi, 2017[79]	2
Tward, 2021[80]	4
Van den Broeck, 2019[81]	3
Whalen, 2016[82]	4
White, 2021[83]	4
Wibmer, 2019[84]	3
Yamoah, 2022[85]	3
Zhao, 2016[86]	2

References

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APPENDIX E. STUDY CHARACTERISTICS

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Badani, 2015b[24] Northeast, USA KQ1 KQ2 Prospective before and after test (own patients) 175	Approximately 2013 No VA patients	Men with very low, low, and intermediate risk who were being considered for active surveillance had Oncotype test run prospectively, questionnaires complete pre and post result	Mean age: 63.9 (7.26) Race: 76.6% White 12.0% Black 5.7% Hispanic 1.3% Asian PSA:NR Gleason: 70.3% Group 1 29.7% Group 2 T stage: 89.2% T1c 10.1% T2a 0.6% T2b	Median Oncotype score: NR Biopsy NCCN 22.2% Very low risk 44.9% Low risk 32.9% Favorable Intermediate	Difference in classification Proportion choosing active surveillance Overall: KQ1 Low ROB KQ2 Serious	Genomic Health
Badani, 2015a[29] ASSESS-D US KQ2 Deidentified case history review with and without test 110 cases; 51 Urologists	NR No VA patients	Consecutive patients presenting with pT3 disease or positive surgical margins after surgery; unavailable prostate tissue or failure to achieve PSA nadir after RP were excluded; urologists were US board-certified recruited from AUA membership directory and high-volume surgeons referred by co-authors	Mean age: NR Race: NR PSA: NR Gleason: NR T stage: NR	Median Decipher score: NR Prostatectomy Clinical risk classification: NR	Change in management/ treatment decision-making Overall: Low ROB	GenomeDx biosciences, national research council of CANADA Industrial Research Assistance Program
Badani, 2013[30] DECIDE United States KQ2 Deidentified case history review with and without test	NR; cases from prior GC validation study in high-risk post-RP men No VA patients	Patients post radical prostatectomy who either had adverse pathology or evidence of biochemical recurrence through PSA	Age range: 57-74 Race: NR PSA: <10: 79%% 10-20: 12.5% >20: 4.1% NA: 4.1% Gleason: 6: 25% (3+4): 25% (4+3): 21%	Mean Decipher score: NR Prostatectomy D'Amico risk groups: Low: 12.5% Intermediate:46% High: 42%	Change in management/ treatment decision-making Overall: Critical ROB	Company (GenomeDx Biosciences)

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24			8: 25% 9: 12.5%% 10: 4.1% T stage: pT2 58.3% pT3 42%			
Berlin, 2019[49] Toronto, Canada KQ3 Retrospective observational	2005 and 2011 No VA patients	Men diagnosed with NCCN-defined IR prostate cancer treated with curative-intent DE-IGRT without neoadjuvant, concomitant, or adjuvant ADT	Median age: 72.4 (Range: 68.4-75.0) Race: NR PSA: 7.8 (Range: 5.7-11.2) Gleason: 1 (3+3) 9.9% 2 (3+4) 62.0% 3 (4+3) 28.1% T stage: cT1c/T2a 78.5% cT2b/T2c 21.5%	Decipher score: Low 72.7% Intermediate 14.9% High 12.4% Biopsy NCCN: Favorable 27.3% Unfavorable 71.9% Unknown 0.8%	Biochemical recurrence-free survival Metastasis-free survival Overall: High ROB	The Terry Fox Research Institute (TFRI),
Bishoff, 2014 [71] USA and Germany KQ3 Retrospective observational Linked paper: Tosoian 2017[56]	Martini-Clinic: 2005-2006, Durham VA 1994-2005, Intermountain HealthCare 1997-2004 VA patients	Patients with localized prostate cancer who underwent radical prostatectomy	Median age: 62 Race: NR PSA median: 6.4 Gleason Less than 7: 58% 7: 35% Greater than 7: 7% T stage T1: 61% T2: 32% T3: 1%	Prolaris: 0 (IQR range –0.9 to 0.9) Biopsy Clinical risk classification: NA	Biochemical recurrence-free survival Overall: High ROB	Undisclosed
Brooks, 2021[39] Cleveland, USA KQ3 Retrospective observational	Between 1987 and 2004 No VA patients	All patients who underwent RP	Mean age: 61 (SD 6) Race: White 82% Black 13% Asia/Hispanic: 5% PSA ≥4: 14% >4-10: 68% >10-20: 13%	Median Oncotype: 26 (19 to 39) Prostatectomy AUA: Low/very low 55% Intermediate 35% High 10%	Metastasis-free survival Prostate-specific mortality Overall: Low ROB	N/A

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			>20: 5% Gleason 3: 62% 3+4: 8% 3+5: 1% 4: 23% 4+3: 3% 4+5: 2% 5, 5+4: 1% T stage T1A: <1% T1B: <1% T1C: 65% T2A: 24% T2B: 7% T2C: 3%			
Canfield, 2017[31] NR US KQ2 Retrospective, comparative cohort before-after testing availability	2013-2016 No VA patients	Patients age >18, AUA low risk, clinical activity for at least 12 months before and 6 months after diagnosis, at least 1 PSA within 12 months before or after dx	Age % ≤50: 2% 50-59: 21% 60-64: 20% 65-69: 22% 70-79: 27% ≥80: 7% Race: NR PSA ≤10: 100% Gleason 6: 100% T stage T1-T2a: 100%	Oncotype score: NR Biopsy AUA: Low risk 100%	Proportion choosing active surveillance Overall: Moderate ROB	Genomic Health Inc (Redwood City, CA)
Canter, 2020[46] USA, New Orleans, LA; Durham, NC; Salt Lake City, UT; Hamburg, Germany KQ3	Martini Clinic-2005-2006; Durham VA-1994-2005; Intermountain-1997-2004; Ochsner Clinic- 2006-2011	Patients with localized prostate carcinoma treated with radical prostatectomy or radiotherapy (external beam radiation +/- androgen deprivation therapy or brachytherapy) with available	Median age: 63 (IQR 58 to 70) Race: Black: 29% Non Black: 71% PSA median 5.9 (IQR 4.5, 9.0) Gleason	Prolaris score median: 0.1 (IQR –0.6, 0.9) Prostatectomy CAPRA: Low: 46% Intermediate: 42%	Metastasis-free survival Overall: Low ROB	

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Retrospective observational	Some VA patients	clinicopathological and molecular data	<7: 46% (3+4): 23% (4+3): 8.4% >7: 12% T stage T1: 69% T2: 29% T3: 2.4%	High: 12%		
Canter, 2019[48] NA New Orleans, LA, USA KQ3 Retrospective observational	2006-2011 No VA patients	Patients with clinically localized prostate carcinoma with available biopsy sample	Median age: 64.5 (IQR range 58, 70) Race: Black 36.6% Non-Black: 63% PSA median: 6.35 Gleason <7: 51% (3+4): 24% (4+3): 10% >7: 15% T stage T1: 73% T2: 23% T3: 4%	Prolaris median score: 0.3 (-0.2, 1.0) Biopsy CAPRA median: 3 (2-5)	Metastasis-free survival Prostate-specific Mortality Overall: Low ROB	Myriad Genetic Laboratories, Inc
Cooperberg, 2015[66] NA Rochester, MN; USA KQ3 Retrospective observational	2000-2006 No VA patients	High risk (PSA >20, Gleason >=8, stage pT3b) prostate carcinoma selected randomly (20% including 11 cases; case cohort) from a population of 1010 patients enrolled prospectively	Median age: 63.5 Race: NA PSA <10: 56% 10-20: 28% >20: 17% Gleason ≤6: 8.1% 7: 49% ≥8: 43% T stage: NR	Decipher score <0.4: 54% 0.4-0.6: 22% >0.6: 24% Prostatectomy CAPRA score <3: 0.5% 3-5: 55% >5: 44%	Prostate-specific mortality Overall: Low ROB	Mayo Prostate Cancer SPORE grant; Richard M. Schulze Family Foundation; National Research Council of Canada Industrial Research Assistance Program, Mayo Foundation For Medical Education and Research and GenomeDx Biosciences Inc.
Cooperberg, 2013[68] NA	1994-2011	Patients with prostate carcinoma who underwent RP without adjuvant or	Median age: 63 Race: NR PSA	Prolaris score: ≤-1: 7% >-1 to 0: 50%	Biochemical recurrence-free survival	Peter R. Carroll, Myriad

Study Study Acronym Country KQ Design Total Enrolled	Cohort Years VA Patients	Patient Enrollment Criteria	Patient Demographics Age Race PSA Gleason T Stage	Test Type Tissue Used Clinical Risk Tool	Outcomes Reported Risk of Bias	Funding and Conflicts
San Francisco, CA KQ3 Retrospective observational	No VA patients	neoadjuvant therapy with >5 years follow-up	≤6: 48% >6 to 10: 30% >10 to 20: 16% >20: 6% Gleason 2 to 6: 52% 7: 42% 8 to 10: 5% T stage: NR	> 0 to 1: 34% >1: 9% Prostatectomy CAPRA-S Low (0 to 2): 63% Intermediate (3 to 5): 28% High (6 to 12): 8%	Overall: Low ROB	
Crawford, 2014[34] NA US KQ2 Prospective pre/post-test result 331	July 19 to December 9, 2013 No VA patients	CCP ordered on patient with documented prostate cancer	Mean age: 67.4 (SD 7.43) Race: NR PSA mean: 7.7 (8.07) Gleason ≤6: 51.7% (3+4): 28.7% (4+3): 12.1% 8-10: 7.5% T stage T1a: 1.5% T1b: 0.3% T1c: 82.5% T2a: 7.3% T2b: 4.2% T2c: 3.9% T3b: 0.3%	Mean Prolaris score: -0.69 (SD 0.82) Biopsy AUA Low: 43.5% Intermediate: 44.1% High: 12.4%	Change in management/treatment decision-making Overall: Serious ROB	Myriad Genetics
Cullen, 2015[65] CPDR (center for prostate cancer research) longitudinal study US KQ3	1990 to 2011 No VA patients	Post RP with NCCN very low, low, intermediate risk	Mean age: 61.0 (SD 7.5) Race: White: 75.9% Black: 20.4% Other: 3.7% PSA <4: 22.9% 4-9.99: 67.9% 10-20: 9.2% Gleason 3+3: 73.4%	Median Oncotype NR Biopsy NCCN Very low: 11.0% Low: 53.6% Intermediate: 35.5%	Biochemical recurrence-free survival Overall: Low ROB	Center for prostate cancer research; uniformed services university of the health sciences; Genomic Health Inc.

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Retrospective observational			3+4: 23.4% 4+3: 3.2% T stage T1: 68.7% T2: 31.3%			
Cuzick, 2012[69] England KQ3 Retrospective observational Linked paper: Cuzick, 2011 [4]	1990 and 1996 No VA patients	Men who had conservatively treated clinically localized prostate cancer, which was diagnosed by use of needle biopsy, were younger than 76 years at the time of diagnosis and had a baseline PSA measurement. Patients treated with or radiation therapy, within the first 6 months after diagnosis, or were excluded	Age: NR Race: NR PSA: NR Gleason <7: 30% 7: 43% >7: 26% T stage T1: 11% T2: 30% T3: 46%	Median Prolaris score: 1.03 (IQR range 0.41 to 1.74) Prostatectomy Clinical risk classification: NR	Prostate-specific mortality Overall: Moderate ROB	Queen Mary University of London
Cuzick, 2015[62] NA UK KQ3 Retrospective observational	1990-2003 No VA patients	Age <76 years at diagnosis and had clinically localized prostate cancer diagnosed by needle biopsy	Age 70.8 (IQR 66.5 to 73.6) Race: NR PSA ≤4: 2.6% >4-10: 30% >10-25: 35% >25-50: 18% >50-100: 14% Gleason 3+3: 26% 3+4: 34% 4+3: 22% >7: 19% T stage NR	Median Prolaris: 0.40 (IQR -0.10 to 1.00) Biopsy CAPRA 0-2: 14% 3-5: 35% 6-7: 23% 8-10: 28%	Prostate-specific mortality Overall: Low ROB	Cancer Research UK, ORCHID, National Institutes of Health (SPORE), the Koch Foundation and Myriad Genetics. This work was supported by Cancer Research UK, Queen Mary University of London, Orchid Appeal, US National Institutes of Health, and Koch Foundation.
Cuzick, 2011[4]	1985-1995 for US	For us cohort: All patients undergoing radical prostatectomy for prostate	Median Age: 68 (IQR 62, 72)	Median Prolaris score: 0.16 (IQR -3.30, 0.64)	Biochemical recurrence-free survival	Queen Mary University of London, NIH

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Temple, Texas, USA, and UK KQ3 Linked paper: Cuzick, 2012[69]	cohort, 1990-1996 for UK cohort No VA patients	cancer. For UK cohort: Men who had clinically localized prostate cancer diagnosed by transurethral resection of the prostate (TURP), were under age 76 years at the time of diagnosis and had a baseline PSA measurement	Race Non-White: 7.3% PSA: 6.9 (4.3, 12.4) Gleason <7: 67.6% 7: 22.8% >7: 9.6% T stage: T1: 33% T2: 67% T3: <1%	Biopsy Prostatectomy Clinical risk classification: NR	Prostate-specific mortality Overall: Low ROB	SPORE, Koch Foundation
Dalela, 2017[57] Various US academic sites and VA KQ3 Retrospective observational	1990-2010 Some VA patients	Patient who had radical prostatectomy with adverse features had Decipher test run to see if adding it to standard adverse clinical features could improve prediction of those that would benefit from adjuvant radiation therapy	Median Age: 61 (IQR 57, 65) Race: NR Median PSA: 8.1 (IQR 5.5 to 12.7) Gleason 3+3: 8.0% 3+4: 43.2% 4+3: 21.9% 8: 11.1% 9-10: 15.4% T stage T2: 27.7% T3a: 39.3% T3b: 28.3% T4: 4.7%	Median Decipher score: 0.41 (IQR 0.26, 0.56) Prostatectomy Clinical risk classification: NR	Time to Clinical Recurrence Overall: Moderate ROB	Unclear (mainly GenomeDx Biosciences)
Dall'Era, 2015[32] NA US KQ2 Retrospective cohort (comparative)	2012-2013 (pre); 2013-2014 (post) No VA patients	Physicians who ordered at least 4 Oncotype Dx tests between May 2013 and Feb 2014 were asked to participate. Those providers then selected at least 7 patients diagnosed with prostate cancer between May 2012 and April 2013, with low or low-intermediate risk prostate cancer, baseline PSA <20, clinical stage T1c-T2c, and	Median age: 64.9 (10.1) Race Black: 16% White: 78% Other: 6% PSA 0 - 4: 27% >4 - <10: 70% 10 - 20: 2% >20: <1% Gleason	Baseline median Oncotype score: 7 (range 4 to 13) GPS group median Oncotype score: 7 (range 1 to 7) Biopsy NCCN: Very low or low: 82%	Proportion choosing active surveillance Overall: Serious ROB	Unknown

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211		no other genomic testing for prostate cancer as the pre cohort. study physicians given eligible cases for GPS (post) cohort	3+3 or less: 85% 3+4 15% T stage T1a/b: 2% T1c: 92% T2a: 4% T2b: 1%			
Den, 2015[63] Philadelphia and Rochester MN, USA KQ3 Retrospective observational 186	1990 and 2009 No VA patients	All patients with pT3 disease and/or positive surgical margins who received post-RP RT	Median age: 61 (IQR 56 to 66) Race: NR Median PSA: 7.8 (IQR 5.3 to 12.3) Gleason ≤6: 14.9% 3+4: 31.9% 7 (4+3): 26.6% ≥8: 25.5% Unknown: 1.1% T stage: NR	Decipher score Low: 39% average: 41% High: 20% Prostatectomy CAPRA-S Low: 5% Intermediate: 50% Hight: 45%	Metastasis-free survival Overall: Low ROB	GenomeDx Biosciences
Erho, 2013[6] NA Rochester, MN, USA KQ3 Retrospective case control	1987-2001 No VA patients	Patients with prostate carcinoma post radical prostatectomy and classified into no evidence of disease group, PSA recurrence group and clinical metastasis group	Age: 66 (IQR 61 to 70) Race: NR PSA: <10: 92 10-20: 33 >20: 50 NA: 11 Gleason ≤6: 9.7% 7: 52% 8: 12% 9: 25% 10: 0.5% T stage pT2N0M0: 40% pT3/4N0M0: 46% pTanyN+M0: 15%	Median Decipher score: NR Prostatectomy Clinical risk tool: NR	Metastasis-free survival Overall Survival Prostate-specific Mortality Overall: Low ROB	National Research Council of Canada, Industrial Research Assistance Program and the Mayo Clinic Prostate Cancer SPORE
Eure, 2017[20]	2014-2015	Patients with low risk prostate cancer	Age <65: 55%	Median Oncotype: NR	Proportion choosing active surveillance	Unclear

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US KQ1 Comparative cohort before (retrospective) and after (prospective) institutional testing 258	No VA patients	recommended to be on active surveillance asked to participate prospectively by getting Oncotype testing and then shared decision making whether to stay on AS	≥65: 45% Race: White 81% Black: 15% Asian: 0.8% Other: 3.4% PSA 0-4: 19% 4.1-9.9: 72% 10-20: 8.7% Gleason 3+3: 75% 3+4: 25% T stage T1c: 87% T2a: 11% T2b: 2% T2c: 0.9%	Biopsy NCCN Very low: 29% Low: 40% Intermediate: 31%	Change classification reclassification Overall: Moderate ROB	

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Feng, 2021[41] NA US and Canada (NRG Oncology Radiation Therapy Oncology Group member sites) KQ3 Prospective observational 760	1998-2003 (study conduct) No VA patients	History of RP with lymphadenectomy at pathologic tumor stage T2 or T3 without nodal involvement, and detectable PSA at least 8 weeks after surgery of 0.2 to 4; karnofsky performance score of 80+, no prior chemo/radiation therapy/hormone therapy other than short period hormonal treatment; no evidence metastasis, no liver disease and had a life expectancy of 10+ years	Median age: 64.5 (IQR 60-70) Race White: 89.2% Hispanic: 1.7% Black: 7.1% Asian: 1.1% American Indian: 0.3% Other 0.6% Median PSA at trial entry: 0.7 (IQR 0.4, 1.1) Gleason 2-6: 29.5% 7: 53.7% 8-10: 16.5% Unavailable: 0.3% T stage T2: 33.5% T3: 66.5%	Median Decipher score: 0.435 (0.28, 0.58) Prostatectomy Clinical risk tool: NR	Metastasis-free survival Overall Survival Prostate-specific mortality Overall: Low ROB	This study was supported by grant from NRG Oncology Operations, grant from NRG Oncology SDMC, grant from NCORP, grant from NRG Specimen Bank, and grant R01 from the National Cancer Institute and Decipher Biosciences.
Freedland, 2013[67] Durham, NC KQ3 Retrospective observational	1991-2006 VA patients	Men who had XRT for prostate cancer and CCP score of their biopsy and regression analysis done to see if CCP score added value above usual clinical parameters of high recurrence risk	Median age: 66 (IQR 60, 71) Race Black: 57.4% Other: 42.6% Median PSA: 0.04 (IQR 5.25, 13.47) Gleason <7: 38.3% 7: 49.6% >7: 12.1% T stage T1: 60% T2: 36.7% T3: 3.3%	Median Prolaris score: 0.12 (-0.43, 0.66) Biopsy D'Amico Low: 27.3% Intermediate: 51.8% High: 20.9%	Biochemical recurrence-free survival Overall: Moderate ROB	Myriad
Gaffney, 2019[17] Northeast US	2015-2018 No VA patients	Patients who had GPS sent out during the 3-year period	Mean age: 65.2 (SD 7.3) Race: NR Mean PSA: 6.5 (3.2) Gleason:	Oncotype Very low: 34.3% Low: 28.4% Intermediate: 36.7%	Change in management/treatment decision-making	Institutional

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
KQ1 Retrospective observational			3+3: 65% 3+7: 35% T stage: NR	High: 0.8% Biopsy NCCN Very Low: 23.1% Low: 33.6% Intermediate 43.3% High: 0%	Change classification reclassification Overall: Moderate ROB	
Glass, 2016[60] Northwest US KQ3 Retrospective observational Linked paper: Spratt, 2017[95]	1997-2009 No VA patients	Decipher test was performed for men undergoing prostatectomy who had high risk features preoperatively (PSA > 20 or GS 8 or higher) or post prostatectomy high risk features pT3 or +SM	Median age: 57 (46, 67) Race White 93.8% Black: 2.2% Other: 4% Median PSA: 6.1 (IQR 4.8, 8.9) Gleason (at RP): ≤6: 39.3% 7: 38.8% 8: 15.6% ≥9: 5.4% Unknown: 0.9% T stage: NR	Median Decipher: 0.32 Prostatectomy CAPRA-S Low: 20.5% Intermediate: 60.7% High: 18.8%	Biochemical recurrence-free survival Clinical Recurrence Overall: Low ROB	Institutional
Gore, 2020[27] USA KQ2 Prospective before-after test (own patients) 246 Linked paper: Gore, 2017[36]	May 2014 to February 2016 No VA patients	Post radical prostatectomy patients being considered for immediate adjuvant radiation therapy (ART) or early salvage radiation therapy (SRT). ART patients had T3 disease. SRT patients had biochemical recurrence after initial nadir post RP (PSA > or equal to 0.2 ng/mL on 2 assessments)	Median age: 63.0 (IQR 48, 74.9) Race White: 89% Other: 11% Unknown: 0.4% PSA at diagnosis: NR ≥10: 25% Unknown: 2% Gleason Group 1: 4.5% Group 2: 47% Group 3: 29% Group 4: 9.8% Group 5: 9.8%	Decipher Low: 39% Intermediate: 24% High: 36% Prostatectomy Clinical risk tool: NR	Addition of ADT to definitive radiation Proportion choosing active surveillance Receipt of adjuvant radiation with or without ADT Overall: Moderate ROB	Decipher Biosciences Inc, San Diego, CA

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			T score pT2: 36% pT3a: 42% pT3b: 13% Unknown: 7.7%			
Howard, 2020 [44] Durham VA KQ3 Retrospective observational	1989-2016 VA patients	VA men who underwent RRP at high risk for recurrence - assessed predictive ability of Decipher compared to CAPRA for metastasis and recurrence, also analyzed by Black race	Median age: 62 (57, 65) Race Black: 55% White: 43% Other: 2% Unavailable: <1% Median PSA: 7.1 (IQR 5.1, 10.8) Gleason 1: 12% 2: 61% 3: 15% 4: 5% 5: 7% T stage pT2: 56% pT3a: 18% pT3b: 18% pT4: 8%	Decipher Low: 51% Intermediate 24% High: 25% Prostatectomy CAPRA-S Low: 10% Intermediate: 62% High: 28%	Metastasis-free survival Prostate-specific mortality Overall: Low ROB	Decipher Biosciences
Karnes, 2018 [54] US multi group study KQ3 Retrospective observational	1987-2010 Some VA patients	Patients who had prostatectomy with adverse pathology retrospectively had Decipher testing to correlate with prostate-cancer-specific mortality	Median age: 62 (IQR 58, 67) Race: NR PSA <10: 55% 10-20: 28% >20: 17% Gleason ≤6: 7% 7: 57% 8-10: 37% T stage: NR	Decipher 0.39 (IQR 0.23, 0.59) Prostatectomy CAPRA-S <3: 19% 3-5: 42% >5: 39%	Prostate-specific mortality Overall: Moderate ROB	DOD/PCRP, Prostate Biorepository Network, Hopkins SPORE, GenomeDx
Klein, 2016 [22]	Between 1987 and 2008	Preoperative prostate-specific antigen (PSA) >20 ng/mL or stage pT3 or	Median age: 62 (IQR 58, 67)	Median Decipher 0.38 (IQR 0.29-0.49)	Change classification reclassification	Many of authors are employees of GenomeDx

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Cleveland/ USA KQ1 KQ3 Retrospective observational Linked paper: Klein, 2015[64]	No VA patients	margin positive or pathologic Gleason score ≥8	Race White: 77.2% Black: 19.3% Asian: 3.5% Median PSA: 6.3 (IQR 5.1, 11.1) Gleason ≤6: 24.4% 7: 24.6% ≥8: 7.0% Unknown: 7.0% T stage T1c: 63.1% T2a: 31.6% T2b: 5.3%	Biopsy Prostatectomy NCCN Low: 40.4% Intermediate: 47.4% High: 7.0% Unknown: 5.3%	Metastasis-free survival Overall: KQ3 Moderate ROB KQ1 Low ROB	Biosciences. Two of the authors received an unrestricted research grant from GenomeDx Biosciences (GENDX1208) to support the costs of this study.
Klein, 2015[64] Cleveland, USA KQ3 Linked paper: Klein, 2016 [22]	1987 and 2008 No VA patients	Preoperative prostate-specific antigen (PSA) >20 ng/ml, stage pT3 or margin positive, and no clinical or radiographic evidence of metastasis or pathologic Gleason score 8; pathologic node-negative disease; undetectable post-RP PSA; no neoadjuvant or adjuvant therapy; and a minimum of 5-yr follow-up for those who remained metastasis free.	Median age: 62 (range 42, 74) Race White: 89.9% Black: 8.3% Asian: 2% Other: 0.6% Median PSA: 6.54 (range 0.1, 66.6) Gleason ≤6: 13.6 7: 62.1 8: 11.8 9: 12.4 T stage: NA	Median Decipher 0.35 (range 0.03, 0.91) Prostatectomy Median CAPRA-S: NR	Metastasis-free survival Overall: Low ROB	GenomeDx Biosciences Inc.
Kornberg, 2019[47] San Francisco, CA, USA KQ3 Retrospective observational	2001-2016 No VA patients	Prostate carcinoma patients on active surveillance who had radical prostatectomy at least 6 months after starting on AS. Participants were diagnosed with Gleason 3 + 3 or low volume 3 + 4 cancer, organ-confined	Mean age: 60.7 (SD 6.8) Race Asian: 2% Black: 2% White: 89% Other: 6% Median PSA: 5.3 (4.2, 7.0)	Median Prolaris 26.4 (18.8, 34.6) Biopsy CAPRA Low: 83% Intermediate: 17%	Biochemical recurrence-free survival Overall: Moderate ROB	Goldberg-Benioff Program in Translational Cancer Research, Genomic Health, Inc. institutional support and United States Department of Defense Prostate Cancer Research

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
		disease, PSA less than 20 ng/ml and a clinical CAPRA risk of 0 to 5.	Gleason: 3+3: 72% 3+4: 28% T stage T1c: 67% T2: 3% T2a: 24% T2b: 3% T2c: 3%			Program Grant W81XWH-13-2-0074
Leapman, 2018 [50] Na San Francisco, CA, USA KQ3 Retrospective observational	Until August 1, 2017 No VA patients	Patients with clinically localized prostate carcinoma who were treated with radical prostatectomy	Median age: 59 (54, 64) Race Native American:<1% Asian/Pacific Islander: 3% Black: 4% White: 84% Mixed: 6% Unknown: 3% Median PSA: 5.9 (IQR 4.6, 8.1) Gleason 1: 64% 2: 23% 3: 6% 4-5: 7% Missing n=17 T stage T1c: 38% T2: 61% T3: 1% Missing n=17	Median Prolaris -0.33 (IQR -0.69, 0.18) Biopsy CAPRA-S Low: 66% Intermediate: 27% High: 28%	Biochemical recurrence-free survival Metastasis or PCSM Overall: Low ROB	Zero Cancer Foundation, Jim Lafferty Memorial Research Grant.
Lehto, 2021[40] NA Finland KQ3	1992-2015 No VA patients	Men treated with RP with pathology showing Gleason score 4 (GS 3+3, 4+3, 4+4) and histopathologic tumor\ stage 2-3; had to have complete clinical data available; no neoadjuvant treatment	Median age- cases: 63 (IQR 9.7) Median age- controls: 62 (IQR 8.0) Race: NR Median PSA- cases: 9.5 (IQR 6.0)	Decipher; Prolaris; Oncotype (Medians NR) Prostatectomy	Metastasis-free survival Prostate-specific mortality Overall: High ROB	Cancer Foundation Finland; Academy of Finland, Hospital Disctrict of Helsinki and Uusimaa, Grant/Award Sigrid Jusélius Foundation

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
			Median PSA- controls: 9.0 (IQR 7.0) Gleason 3+4: 39% 4+3: 41% 8: 20% T stage T2 35% T3a: 34% T3b: 31%	Clinical risk tool: NA		
Leon, 2018[51] NA France KQ3 Retrospective observational	2000-2007 No VA patients	Patients post RP for prostate cancer	Median age: 63 (IQR 58, 67) Race: NR Median PSA: 8.0 (IQR 5.8, 11.0) Gleason <7: 36% 3+4: 30% 4+3: 27% >7: 7% T stage: NR	Median Prolaris score: 0.08 (IQR –0.36, 0.57) Prostatectomy Median CAPRA-S: 3 (IQR 1, 4)	Biochemical recurrence-free survival Overall: High ROB	Myriad Genetics
Lynch, 2018[18] 6 US VAMCs KQ1 KQ2 cohort before/after test availability 390	Retrospective: January 2014 and March 2015. Prospective: March 2015 and February 2016 VA patients	Newly diagnosed NCCN very low, low, intermediate risk prostate cancer; intermediate had Gleason 3+3, PSA 10-20 or bx Gleason 3+4 with 3 or fewer pos biopsy cores and 33% or less positive cores for tumor and PSA less than 20; for prospective cohort - had not yet made a management decision	Median age: 66 (range 43, 83) (untested) 66 (range 50-85) (tested) Race: White: 75% Black: 17% Other: 6.9% PSA: NR Gleason 3+3: 69% 3+4: 31% T stage: NR	Median Oncotype 26.5 (range 0, 61) Biopsy NCCN Very low: 20% Low: 40% Intermediate: 40%	Change in management/treatment decision-making Proportion choosing active surveillance Change classification reclassification Overall: KQ1 Low ROB KQ2 Moderate ROB	Genomic Health Inc, the company that has exclusive rights to conduct the 17-gene Genomic Prostate Score assay. Funding was provided to the Veteran Healthcare Administration, not to individual authors
Michalopoulos 2014[26] US	2013 No VA patients	Patients who underwent radical prostatectomy in a community-based practice and who presented	Median age: 63 (IQR 59, 67) Race: NR PSA	Median Decipher probability of metastasis: 4.2% (IQR 2.8, 9.6%)	Recommended treatment for post-surgery clinically high-risk patients vs observation	GenomeDx Biosciences

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
KQ1 KQ2 Prospective before-after test (own patients) 146		adverse pathological findings	<10: 79.5% 10-20: 12.3% >20: 8.2% Gleason 6: 13.7% 3+4: 37% 4+3: 29.4% 8: 8.9% 9: 9.6% 10: 0.7% Unknown: 0.7%	Prostatectomy CAPRA-S Low: 16.4% Intermediate: 55.5% High: 21.9% Unknown: 6.2%	Change classification reclassification Overall: KQ1 Low ROB KQ2: Serious ROB	
Morris, 2021[33] NA USA KQ2 Retrospective comparative cohort before/after initiation	2015-2018 No VA patients	Localized Prostate cancer patients with CCP results (and mpMRI/US, PI-RADS score) from a single practice; 2 cohorts - one newly diagnosed and one "on AS"	Median age: 68 (IQR 62, 72) Race: NR Median PSA: 7.6 (IQR 5.4, 11.7) Gleason <7: 39.6% 3+4: 40.5% 4+3: 18.0% >7: 1.8% T stage: NR	Median Prolaris score –0.5 (IQR -0.9, 0.0) Biopsy NCCN: Low: 32.9% Favorable Intermediate: 24.3% Unfavorable Intermediate: 34.7% High: 8.1%	Treatment selection (binary AS or definitive treatment, definitive treatment includes ADR, radiation and or RP) Overall: Moderate ROB	NR
Murphy, 2021[23] Illinois KQ1 KQ2 Randomized trial 200	Not disclosed Some VA patients	Men with new diagnosis of low to favorable intermediate-risk prostate cancer	Median age: 63.6 (6.6) Race Black: 70.0% European American: 16.5% Hispanic or Latino: 12.5% Asian: 1.0% PSA: 5.98 (SD 2.44) Gleason (3+3): 81% (3+4): 19% T stage: NR	Median Oncotype: NR Biopsy NCCN Very low: 40% Low: 35% Low intermediate: 25%	Proportion choosing active surveillance Change classification Overall: High ROB	Biomarker Development Award, DOD, Prostate cancer Research Program

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Nguyen, 2017a[55] Boston, MA; Baltimore, MD; Ann Arbor, MI; San Diego, CA; San Francisco; CA; Cleveland, OH; Houston, TX; Miami, FL KQ3 Retrospective observational	1987-2014 No VA patients	Two cohorts were selected: Patients with intermediate or high risk NCCN prostate carcinoma treated with first line RT and/or ADT. Patients of prostate carcinoma with adverse pathology on RP	Median 64 (IQR 58, 70) Race: Black: 14% Arabic: 0.43% Asian: 1.7% White: 71% Hispanic: 1.3% Other: 12% PSA: 7 (IQR 4.6, 13.2) Gleason Grade group 1 19% Grade group 2 28% Grade group 3: 25% Grade group 4: 14% Grade group 5: 15% T stage ≤T1c: 46% ≥T2a: 53% Unknown: 0.85%	Median Decipher: 0.39 Biopsy NCCN Low: 11% Intermediate: 54% High: 32% Unknown: 3%	Metastasis-free survival Overall: High ROB	GenomeDx Biosciences, The Wood Foundation, Freeman Family, Fitz's Cancer Warriors, David and Cynthia Chapin, Hugh Simons in honor of Frank and Anne Simons, The Campbell Family in Honor of Joan Campbell, Scott Forbes and Gina Ventre Fund, the Baker Family, Prostate Cancer Foundation, and a Grant from an Anonymous Family Foundation.
Nguyen, 2017b[58] NA Boston, MA, USA KQ3 Retrospective observational	2001-2013 No VA patients	Patient with intermediate and high risk NCCN prostate carcinoma treated with radiation and ADT	Median: 67 (IQR 60, 71) Race Black: 16% White: 79% Other: 5% Median PSA: 7.3 (IQR 4.7-14.9) Gleason ≤6: 7% 3+4: 23% 4+3: 36% 8: 15% ≥9: 19% T stage ≤T2a: 64% ≥T2b: 35%	Median Decipher: 0.39 (IQR 0.22- 0.61) Biopsy NCCN Intermediate: 55% High: 45%	Biochemical recurrence-free survival Metastasis-free survival Overall: Moderate ROB	Anonymous Family Foundation, the Prostate Cancer Foundation, Fitz's Cancer Warriors, Cynthia and David Chapin, Hugh Simons in Honor of Frank and Anne Simons, The Gina Ventre and Scotty Forbes Fund, The Campbell Family in Honor of Joan Campbell and GenomeDx Biosciences
Nguyen, 2015[28] Na	N/A	Physicians responding to emails invitations were eligible for study. Self-identified genitourinary	Median age 61 (IQR NR) Race: NR PSA	Median Decipher: NR Prostatectomy	Change in management/treatment decision-making	GenomeDx Biosciences and the National Research Council Canada

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Multicenter, USA KQ2 Deidentified case history review with and without test 46		radiation oncologists using ASTRA directory that provide consultation to at least 80 prostate carcinoma patients per year. Urologists were identified using AUA directory that performed at least 40 RPs per year	<10: 90.0% ≥10: 9.1% Gleason 6: 18.2% 3+4: 36.3% 4+3: 9.1% 8: 9.1% 9: 18.2% 10: 9.1% T stage: pT2N0M0: 45.5% pT3N0M0: 54.5%	D'Amico risk groups Low: 18.2% Intermediate: 36.4% High: 45.4%	Overall: Moderate ROB	Industrial Research Assistance Program (grant no. 765817). Partial support was also provided by the Prostate Cancer Foundation, David and Cynthia Chapin, Fitz's Cancer Warriors, Frank and Anne Simons, and a grant from an anonymous family foundation.
Oderda, 2017[21] NA Italy KQ1 Retrospective observational	RPs 2013-2015 No VA patients	Newly diagnosed cases of prostate cancer with analyzed biopsy and had a successful prior RP	Mean age: 67.7 (SD 6.5) Race: NR PSA 9.6 (SD 12.6) Gleason 6: 30.8% 7: 48.0% 8-10: 21.2% T stage T2: 55.8% T3: 44.2%	Prolaris score -0.16 (0.72) Biopsy EAU Low: 25.0% Intermediate: 46.1% High: 28.8%	Change classification reclassification Biochemical recurrence-free survival Overall: High ROB	NR
Ramotar, 2022[42] Toronto Canada and Philly US KQ3 Retrospective observational	N/A No VA patients	Men diagnosed with prostate cancer, treated with maximal local therapies (RP and PORT), and having pathology slides available for review.	Median age: 61.5 (42, 77.2) Race: NR Median PSA: 7.6 (0.4, 165.4) Gleason 1:11.2% 2: 37.9% 3: 29.1% 4-5: 21.8% Number Missing: 15 T stage: NR	Decipher Low: 21% Intermediate: 29% High: 50% Biopsy Prostatectomy CAPRA-S 0-2: 10.4% 3-5: 44.3% ≥6: 45.4% Number missing: 119	Biochemical recurrence-free survival Overall: High ROB	Internal funding (through department funds).).

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Rayford, 2018[25] NA USA KQ1 Retrospective observational	NR	Tissue from urologic oncology community practice in Memphis, TN obtained from biopsy samples.	Median Black age: 66 (61, 71) Median White age: 65 (60, 71) Median Black PSA: 5.6 (4.0, 8.8) Median White PSA: 4.8 (3.6, 6.9) Gleason <7: 30% 3+4: 49% 4+3: 1.9% >7: 19% T stage T1c: 83% T2: 15%	Median Prolaris (Black): 3.5% Median Prolaris (White): 3.1% Biopsy AUA Low: 26% Intermediate: 41% High: 33%	Change classification reclassification Overall: Moderate ROB	NR
Ross, 2016a[59] 3 academic centers and 1 VA (Hopkins, Mayo, T Jeff, and DVAHCS) KQ3 Retrospective observational	1990-2010 Some VA patients	After radical prostatectomy, patients with adverse pathologic features had adjuvant RT, RT for minimal PSA disease, RT with higher PSA recurrence compared against patients with no RT at all before the development of metastasis	Median age: 61 (range of IQR 57, 66) Median PSA 8 (range of IQR 5.2, 15.5) Race: NR Gleason ≤3+4: 55% 4+3: 22% 8: 11% ≥9: 12% T stage: NR	Median Decipher: NR Biopsy CAPRA-S: NR	Metastasis-free survival Overall: Moderate ROB	Unclear

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Ross, 2016b[61] NA USA, Hopkins KQ3 Retrospective observational Linked paper: Spratt, 2017[95]	1992-2010 No VA patients	Patients post prostatectomy with localized intermediate or high-risk disease, undetectable PSA after surgery, and no postoperative treatment until the development of metastatic disease	Median age: 60 (56, 64) Race White: 88.8% Black: 8.1% Other: 1.9% Unknown: 1.2% PSA 9.5 (IQR 6.2, 14.2) Gleason ≤6: 26.2% 7: 53.3% 8: 13.8% ≥9: 6.2% T stage: NR	Median Decipher: 0.34 (IQR 0.22, 0.52) Prostatectomy Clinical risk tool: NR	Metastasis-free survival Overall: Moderate ROB	Investigator and Genome Dx Bioscience
Seiden, 2021[16] Brooklyn, New York KQ1 Retrospective, single Institution 63	2016 -2020 No VA patients	Black men with low or intermediate risk prostate cancer who would otherwise be managed with active surveillance	Median age: 66 (IQR 61, 69) Race: NR Median PSA 44 (IQR 28, 60) Gleason 3+3: 76% 3+4: 24% T stage T1a: 17% T1b: 10% T1c: 51% T2a: 6% T2b: 2% T2c: 10% NA: 5%	Median Oncotype: 25% (IQR 19, 34) Biopsy NCCN Very low: 11% Low: 28% Favorable Intermediate: 49% Unfavorable Intermediate: 2%	Change classification reclassification Overall: Moderate ROB	None
Shahait, 2021[37] NA KQ1 KQ3 USA	2013- 2018 No VA patients	Patients with prostate cancer were treated with radical prostatectomy, adverse pathological features and had post prostatectomy genomic classifier test information	Median age: 63.6 (IQR 58, 68) Race: NR Median PSA: 5.8 (IQR 4.5, 8.48) Gleason 1: 2% 2: 52% 3: 30%	Median Decipher: 0.59 (IQR 0.41, 0.72) Prostatectomy Median CAPRA-S: 5 (IQR 3, 6)	Risk Stratification Time to secondary therapy Overall: Moderate ROB	None

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
Prospective observational			4:11% 5: 6% T score: NR			
Shangguan, 2020[45] NA China KQ3 Retrospective observational	2010-2014 No VA patients	Adverse pathology (seminal vesicle invasion, extracapsular extension, positive surgical margins), post radical prostatectomy at a single institution	Median age: 68 (IQR 64, 73) Race: NR Median PSA: 15.3 (10.3, 26.0) Gleason ≤6: 26% 7: 55% ≥8: 19% T score: NR	Median Prolaris: 0.45 (IQR 0.3, 1.3) Prostatectomy CAPRA-S Low: 10% Intermediate: 44% High: 46%	Biochemical recurrence-free survival Overall: High ROB	National natural science foundation of China; shanghai municipal education commission-gaofeng clinical medicine grant support
Shore, 2016[35] USA KQ2 Prospective registry before/after test 1596	Not reported No VA patients	Patients were newly diagnosed with prostate cancer within the past 6 months, untreated, with sufficient biopsy tissue; presumed clinically localized	Mean age: 65.9 (SD 8.36) Race Black: 8.9% Asian: 2.8% Alaska Native/ Pacific Islander: 0.4% White: 77% Latino/Hispanic: 9.1% Mixed: 0.3% Other: 0.5% Unknown: 1.0% Mean PSA: 7.8 (SD 8.15) Gleason 6: 47.8% 3+4: 27.9% 4+3: 11.9% 8: 8.3% ≥9: 4.1% T stage T1a: 1.2% T1b: 0.6% T1c: 72.1% T2a: 13.9% T2b: 6.4% T2c: 4.7%	Mean Prolaris: -0.7 (Range -2.8, 2.0) Biopsy AUA Low: 40.2% Intermediate: 42% High: 17.7%	Change in management/treatment decision-making Overall: Moderate ROB	Myriad Genetics

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
			T3a: 1.0% T3b: 0.1%			
Spratt, 2018a[52] Houston, Durham, Philly, USA KQ3 Retrospective observational	1990 and 2015 Some VA patients	To have undergone RP, sufficient tissue for genomic analysis, and serial PSA measurements post-RP to document undetectable versus persistently detectable PSAs postoperatively	Median age: 60 Race Black: 21% White: 73% Other: 4.6% Unknown: 0.8% Median PSA: 6.4 Gleason 1: 6.7% 2: 46% 3: 33% 4: 7.1% 5: 6.7% Unknown: 0.4% T stage T2: 48% T3a: 28% T3b: 21% T4: 1.6% Unknown: 0.8%	Decipher Low: 46% Intermediate: 28% High: 26% Prostatectomy CAPRA-S Low: 26% Intermediate: 43% High: 26% Unknown: 6%	Metastasis-free survival Overall: Moderate ROB	GenomeDx Biosciences
458 Spratt, 2018b[19] USA KQ1 KQ3 Prospective observational 6,928	1997-2016 No VA patients	Patients with either biopsy or radical prostatectomy tissue for localized prostate cancer with exclusion of patients having received neoadjuvant treatment.	Median age: 64 (IQR 58, 70.0) Race Black: 13.6% White: 71.1% Other: 4.2% Unknown: 11.1% Median PSA: 7.0 (IQR 4.6, 13.2) Gleason 3+3: 18.7% 3+4: 27.7% 4+3: 25.1% 8: 13.6% 9-10: 14.9 T stage	Median Decipher: NR Biopsy Prostatectomy NCCN Low: 9% Intermediate- favorable: 15% Intermediate-unfavorable: 40% High/very-high: 35% Unknown: 1.3%	Change classification reclassification Metastasis-free survival Overall: KQ1 Low ROB KQ3 High ROB	DOD and Prostate Cancer Foundation Young Investigator Award

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
			T1: 46% T2: 44% T3/4: 8% Unknown: 1.7%			
Tosoian, 2020[43] NA USA KQ3 Retrospective observational	1995-2005 Some VA patients	NCCN high-risk and VHR who underwent GC testing; high risk = T3a or GG 4-5 or PSA >20; VHR = T3b-T4 or Gleason pattern 5; no neoadjuvant ADT or evidence nodal disease prior to RP	Median age: 62 (IQR 56, 69) Race: NR Median PSA 15.2 (6.37, 25.8) Gleason 1: 14.6% 2: 13.6% 3: 8.9% 4: 35.8% 5: 22.5% Unavailable: 4.7% T stage T1: 27.7% T2: 48.1% T3/4: 17.8% Unavailable: 6.4%	Decipher Low: 46.2% Intermediate: 22.5% High: 31.4% Biopsy Prostatectomy NCCN High-risk: 75.8% Very high-risk: 8.6% Unavailable: 15.5%	Metastasis-free survival Overall: Low ROB	Decipher Biosciences
Tosoian, 2017[56] USA KQ3 Retrospective observational 91 Linked paper: Bishoff 2014[71]	1994- 2006 VA patients	Patient with NCCN low-risk prostate cancer who underwent radical prostatectomy	Median age: 61.4 (IQR 57, 65.7) Race: NR Median PSA: 5.7 (4.4, 7.8) Gleason: NR ≤6: 100% T stage T1c: 69.5% T2a: 24.6% ≥T2b: 5.6%	Median Prolaris: -0.15 (IQR -0.7, -0.4) Biopsy CAPRA Low: 74.6% Intermediate: 25% High: 0.4%	Biochemical recurrence-free survival Overall: High ROB	DOD PRTA award, PCF Young Investigator Award, Patrick Walsh Investigator Grant
Van Den Eeden, 2018[53]	1995-2010 No VA patients	Men who had radical prostatectomy with sufficient follow up underwent GPS testing	Median age: 61 (IQR 57, 65) Race White: 79%	Median Oncotype: NR Biopsy	Biochemical recurrence-free survival Metastasis-free survival	Institutional

Study **Study Acronym** **Country** **KQ** **Design** **Total Enrolled**	**Cohort Years** **VA Patients**	**Patient Enrollment Criteria**	**Patient Demographics** **Age** **Race** **PSA** **Gleason** **T Stage**	**Test Type** **Tissue Used** **Clinical Risk Tool**	**Outcomes Reported** **Risk of Bias**	**Funding and Conflicts**
USA, West Coast (CA) KQ3 Cross-sectional 279			Black: 11% Other: 10% PSA 0-4: 9.5% 4.1-10: 70.1% ≥10.1: 20.4% Gleason: 3+3: 38% 3+4: 46% 4+3: 11% 4+4: 2.7% Any 5: 2.8% T stage T1: 25% T2: 75% T3: 0.4%	NCCN Very low: 3% Low: 21% Intermediate: 67% High: 9.3%	Prostate-specific mortality Overall: Low ROB	
Vince, 2021[38] NA US KQ3 Prospective observational 855	2015-2019 No VA patients	Clinically localized prostate cancer who underwent testing as part of routine clinical care and were able to be matched with Decipher GRID registry; for AS analysis - clinicians had to have explicitly stated in medical records that AS is primary management strategy and could not have received definitive treatment within 6 months of diagnosis	Median age 66 (60, 72) Race Black: 13.1% Asian: 0.9% Native American: 0.1% White: 75% Unknown/other: 11% PSA 6.1 (IQR 4.4, 9.2) Gleason 1: 21.9% 2: 36% 3: 23.1% 4-5: 19% T stage T1: 72% T2: 26.4% T3/4: 2%	Median Decipher: NR Biopsy NCCN Low: 19.1% Favorable-intermediate: 30.8% Unfavorable-intermediate: 40% High: 10%	Time to Treatment Time to Treatment Failure Overall: Low ROB	Blue cross blue shield of Michigan, department of defense physician research training award, Adlfred A Taubman Institute; Prostate cancer Foundation, NCI

APPENDIX F. PEER REVIEW DISPOSITION

Question Text	Reviewer Number	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	
	2	Yes	
	4	Yes	
	5	Yes	
	7	Yes	
Is there any indication of bias in our synthesis of the evidence?	1	No	
	2	Yes - The bias is more so a lack of appreciation of the current flaws in risk stratification that are well documented, acknowledged even in NCCN guidelines, and the purpose of prognostic biomarkers are to improve risk stratification to enable select treatment decisions to be personalized.	We agree that there are limitations in currently used clinical risk stratification schemes and that there is a need for better evidence-based ways to accurately assess patient prognosis and personalize treatment plans. The purpose of this review was to assess the prognostic ability of genomic classifier tests based on existing evidence. This evidence synthesis can inform clinical determinations of whether or not genomic classifier tests should be incorporated into prostate cancer management with the goal of improving prognostic assessment and treatment planning. We have edited language in the introduction and discussion to clarify the

			rationale for this review and to acknowledge the limitations of existing schemas.
	4	No	
	5	No	
	7	No	
Are you aware of any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?	1	No	
	2	Yes - The following randomized trials have been performed and reported with Decipher but not all included: i. RTOG 0126 ii. RTOG 9202 iii. RTOG 9413 iv. RTOG 9902 v. RTOG 9601 vi. SAKK 09/10 vii. SPARTAN viii. TITAN ix. CHAARTED x. STAMPEDE	We have reviewed the listed studies identified by the reviewer and considered them with respect to our eligibility criteria. To be included in this report, studies had to evaluate one of three *a priori* identified genomic classifier tests evaluated in localized prostate cancer and published in full manuscript form in a peer reviewed journal from 2010 to 4/20/2022 (see Table 1 for full eligibility criteria). Please see below for a detailed review and clarification on why these studies were not included and identification of the one that was included: i. analysis related to Decipher reported as abstract only as ASCO GU 2/2022. No full manuscript available. Does not meet inclusion criteria

		ii/iii/iv. data from these trials were analyzed together in an article that was published after search date; have identified in discussion (see “ongoing work”) v. this study was included in our review (Feng et al.2021) vi. published after our search date; identified in discussion (see “ongoing work”) vii. identified by our search but excluded for not meeting population eligibility criteria (castrate resistant prostate cancer with secondary biochemical recurrence) viii. analysis related to Decipher was presented as an abstract at ASCO 2020 and is not currently available as peer reviewed manuscript; also would not meet population eligibility criteria (metastatic prostate cancer) ix. identified by our search but excluded for not meeting population eligibility criteria (metastatic prostate cancer) x. release as preprint after our search date. Identified in

			the discussion (see “ongoing work”).
	4	No	
	5	No	
	7	No	
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	1	appreciated the recommendations re areas for further research	We are glad those were found useful.
	2	1. Problems with the way endpoints were used to assess benefit: a. The panel used the following metrics to assess benefit of a biomarker: i. Risk reclassification 1. Reclassification to what from what? If you are saying a patient has NCCN intermediate risk disease and then has Decipher High, is this reclassification? If so this is problematic. The cutpoints used for Decipher for example have nothing to do with NCCN risk groups. In contrast, we have used prospective data to determine the reclassification from NCCN to a new integrated “clinico-genomic” model that combines NCCN and Decipher and that reclassified 67% of patients (Spratt JCO 2018). However, what is reported in this report says 21-51% and I don’t know how that was calculated.	We appreciate the concerns about risk reclassification assessment. Existing clinical risk classification systems and genomic classifier test systems use the same language for risk classification despite stemming from different data. This key question was included to clarify to what extent genomic classifier tests offer different risk classifications from commonly used clinical risk classification systems such as NCCN. We included studies that assessed change in risk assessment with a genomic classifier test in a number of ways (including direct comparisons and integration of genomic classifier results with existing clinical risk stratification schemes such as in the example noted by the reviewer). We acknowledge that the different ways that reclassification is assessed

		and interpreted in the existing literature is a limitation and hinders summarization across studies. To provide clarity, we have added additional detail about our methodologic approach for this key question. In addition, we added this limitation to the discussion section. Regarding the reported reclassification rate from Spratt et al. JCO.2018. We abstracted the data reported in Table 4 from Figure 4a and 4b in the article which is closer match to the data available from other studies in this report. We have verified the accuracy of the abstracted numbers as reported in the article. We have added reclassification findings from the second biopsy cohort that showed change from the 6-tier NCCN risk group to the 6 tier combined clinical-genomic risk group in the text (page 31) which is the cohort with 67% reclassification as mentioned by this reviewer.
2	2. Additionally, reclassification of >10% is very meaningful to patients if that changes how they would be treated. If 1 out of 10 men were classified as intermediate risk and now as low risk and don't need treatment, that is powerful. Very few tests we order reclassify a patient the majority of the time. A bone	We agree that understanding what level of change in classification would be clinically meaningful is important context. Moreover, the threshold for what is

	scan in high risk disease reclassifies a patients stage ~5% of the time.	clinically meaningful is not the same from one clinical context to another or even one test to another. To our knowledge, there is not an existing, well-established threshold for what is a clinically meaningful change in risk classification for patients with localized prostate cancer. This together with the fact that we found a range of reclassification rates rather than a clear estimate rate raises challenges for synthesis across studies. We have adjusted our language in the results to reflect the uncertainty in the clinical meaning of our findings. Note that we did not explicitly consider the impact of risk reclassification on changes in treatment selection. This was not regularly reported, though a few studies reported occurrence of this secondary step after risk reclassification (see Gore 2017 and Gore 2020).
2	ii. Treatment recommendation change 1. The panel does not seem to appreciate the other biomarkers and tests done routinely change management <10% of the time, and a change of >10% is huge. Example, CT and bone scan change management ~5% of the time in men with localized prostate cancer. PSMA PET/CT changes stage of the disease 10-20% of the time. As shown in the	We appreciate that we may have mischaracterized the importance of the findings around the change in treatment management in response to test results as it relates to potential clinically

	systematic review from Jairath et al, European Urology 2021, the number needed to test for patients from the multiple Decipher studies are all <10 to change management in 1 patient. Often they are NNT of 3-4.	meaningful threshold in terms of changes in management after testing. We note that similar to reclassification discussed above, we are unaware of an explicit agreed upon threshold for this outcome. We have adjusted our wording accordingly.
2	2. This endpoint [change in management] itself is problematic, and a major criticism of the approval of many imaging tests, as changing management doesn't mean it is helping a patient. One must show the test is independently prognostic and that the added information enables an informed change in management.	As noted above, we agree that change in management as an endpoint has significant limitations as this reviewer mentioned and must be considered in conjunction with evidence demonstrating the tests prognostic ability. We have expanded this limitation in the discussion (see "clinical implications", KQ2).
2	iii. "Prognostic information" 1. This is the crux of what "prognostic" biomarkers aim to do. Improve risk stratification and prognostication. We have published in Spratt et al, JCO 2018 a very large improvement of NCCN vs NCCN+Decipher (clinicogenomic model), as have others (Berlin et al, IJROBP). The improvement in AUC/C-index is quite large (10%-20%+ improvement in accuracy). That accuracy is what enables changes in management (as is now noted in NCCN guidelines under the Risk Stratification section).	We acknowledge that NCCN guidelines include mention of use of genomic classifier testing and have noted this in our appendix which highlights recommendations about these 3 genomic classifier tests in current clinical guidelines (see Appendix A).
2	The sole reason we no longer give ADT to all men with intermediate risk prostate cancer getting RT is because of a moderately good prognostic model was built by me and my co-resident at the time, Dr. Zumsteg, to create what is now called favorable vs unfavorable intermediate risk (used around the world and in NCCN guidelines). All this system did was divide patients into lower and higher risk of recurrence which changed the absolute (not relative) benefit	To date analysis of RTOG 0126 with respect to Decipher has only been published in abstract form. As noted above, our eligibility criteria required full peer-reviewed publications for eligibility. We added a

	of ADT. Decipher adds to that majorly to identify ultra-low risk patients (Berlin et al, IJROBP showed no men with mostly unfavorable intermediate risk who got RT alone developed mets with Decipher low; RTOG 0126 we showed that Decipher low patients had only a 4% risk of mets at 10 years with RT alone, but a 16% risk of mets for Decipher high patients).	note to the discussion (see "ongoing work") that more evidence is likely forthcoming in the literature. The study by Berlin noted by the reviewer was included in this review and is considered within the context of the breadth of literature identified. Of note, Berlin et al indicate the need for a prospective clinical trial which is currently underway (GU010); this trial is listed in appendix 5.
2	2. Data used a. The following randomized trials have been performed and reported with Decipher but not all included: i. RTOG 0126 ii. RTOG 9202 iii. RTOG 9413 iv. RTOG 9902 v. RTOG 9601 vi. SAKK 09/10 vii. SPARTAN viii. TITAN ix. CHAARTED x. STAMPEDE	Thank you for bringing these to our attention. Please see our above response regarding these trials individually.
2	3. Assessment of quality a. This review/summary paper will be criticized majorly given the Simon criteria, the most widely used criteria to assess the quality of prognostic biomarkers, would state Decipher is level 1-2 and Prolaris and Oncotype are 3. However, the panel states the evidence for Decipher is low and Prolaris and Oncotype are very low. How is having >40 studies, >10 completed RCTs profiled, show "low" evidence for Decipher? NCCN guidelines classifies it as level 1 evidence now.	The certainty of evidence statement reflects a determination of the totality of the existing evidence with consideration of how it applies to the specific question at hand. This incorporates but is not equivalent to the quality (or risk of bias) assessment of each individual study. The

		certainty of evidence determination is driven by GRADE criteria which is the current standard for systematic reviews. For this review, we frequently downgraded our assessments due to the fact that most all identified studies were older and included patients that received during a distinctly different practice era from current modern management options. In addition, our assessments were downgraded for considerations such as inconsistency of effects (i.e. variation across included studies) and imprecision (i.e. wide confidence intervals in setting of relatively few events). Thus, it is possible to have a large number of relevant studies but still have low certainty of evidence as it relates to the specific question driving the review.
4	Some comments: 1) what percent risk reclassification would the panel consider to be significant to recommend genomic testing using any of the validated panels? Key finding bullet 2 suggests that a significant minority of men DO have risk reclassification, and while not the majority, this could still be important for up to 40% of men! There is a general lack of any thought or opinion here on what rate of reclassification is significant and would be of interest to the panel, particularly if the genomic classification has more prognostic value than the clinical NCCN classification. Suggest revisions to KQ1.	As noted above, we agree that the determination of what is a clinically significant determination of risk reclassification is driven by clinical practice standards rather than the existing data. We appreciate that we did not frame this part of the discussion accurately and have reworded the implications of this

		percentage accordingly as noted above.
4	2) The evidence for the DECIPHER to provide more than just a prognostic effect in the salvage RT setting seems stronger than other settings and for other biomarkers/genomic classifiers, based on the phase 3 RTOG 9601 trial (Feng F et al JAMA Oncol 2021). For example, men with low PSA values <0.7 in the early salvage post RP setting and with a low risk DECIPHER profile had no benefits and potential harms from hormonal therapy with salvage RT, while those with a high risk DECIPHER profile had a survival benefit. This really deserves more attention and recommendation in my opinion given the phase 3 controlled setting with long term follow up and potential clinical utility to VA patients and cost savings/QOL impact on veterans who may be able to avoid 2 years of hormonal therapy and the low harms of performing this classifier on RP tissue. Data is not strong here for other classifiers in the salvage RT setting. Suggest revisions to KQ2 post RP especially around p45 and 56. Adjuvant RT is seldom offered anymore, but early salvage RT is. This randomized trial and study is not even discussed in KQ2. Suggest this remains relevant to men with localized PC and management decision making post-RP for those with PSA recurrence. If the authors wish to avoid this setting, this needs to be clearly discussed still as outside of the scope of the questions around initial management, but I think the panel should take this on. Limiting itself to just discussions around reclassification and prognostic importance misses this important aspect of clinical utility where in my opinion is the ONLY setting where a genomic classifier has demonstrated clinical utility.	We appreciate the reviewer's interest in evidence about response to treatment among patients with different classifier identified risk levels. However, this was not within the scope of this review as designed with those who nominated this work. KQ2 asks if treatment decisions were changed based on the results of receipt of test results and is not structured to evaluate if patient outcomes vary by treatment received depending on genomic classifier test risk stratification. We have added explicit notation of this in the discussion (see 2nd paragraph of Limitations). This issue may be an appropriate focus for a future review.
4	3) Perhaps a statement about pathology AI biomarkers being outside of the scope of this report on genomic classifiers? This could be the subject of a separate review given emerging evidence on the clinical utility of the Artera AI pathology biomarker across several contexts for prognosis and prediction of hormonal therapy benefit in a radiation oncology context (intermediate risk PC).	AI based biomarkers, whether based on pathology, radiomics, or other datasets, are outside the scope of this current review but could be considered in the future when sufficient primary data is available. We have noted this as suggested in our

		discussion section (see “limitations”)
4	4) The panel could speculate on what the potential harms are for performing a genomic classifier. The test does not require a new biopsy or ANY direct harms and does not disclose ANY genetic or familial risk or PHI disclosure. The only harms are really the costs. The costs should be discussed therefore within the VA, as compared to the benefits and cost savings, for example of avoiding unnecessary treatment like 2 years of ADT.	We agree that this is an important consideration for contextualizing the findings in this review. We have added a statement about the issue of harms from this test as suggested in our discussion (see first paragraph).
5	The prostate Oncotype scare is no longer owned by Exact Sciences and is now owned by MDX and renamed Prostate GPS as they were not allowed to use the name Oncotype when they purchased it.	Thank you for this clarification.
7	This is an excellent analysis that is very appropriate for the "moment". It does an outstanding job of addressing the key questions in a way that is comprehensive, unbiased, relevant and useful. It far exceeded my expectations.	Thank you.

APPENDIX G. ONGOING STUDIES

Test Trial Name (Short) Projected N	Full Trial Name	Objective	Study Design Follow-up	Outcomes Measured	Status/Projected Completion
Prolaris NCT03152448 1511 *VA based study	Prospective Prolaris Value and Efficacy (P-PROVE)	To measure the impact on first-line therapy of genomic testing of biopsy tissue from recently diagnosed treatment-naïve patients with early stage localized prostate cancer.	Prospective observational 5 years	• Effect on treatment • Biochemical recurrence • Progression to interventional treatment	Terminated- “Myriad has sufficient data to do an analysis on the primary objective, durability, and has made the decision not to continue collecting data for the other study objectives.”
Decipher NCT02783950 356	Genomics in Michigan Impacting Observation or Radiation (G-MINOR)	To determine the impact of Decipher test results on adjuvant treatment decisions of high-risk post-RP patients with undetectable post-op prostate specific antigen (PSA) compared to clinical factors alone.	Parallel assignment Interventional 5 years	• Number of participants that receive Adjuvant treatment • Time to Adjuvant treatment • Time to salvage treatment administration • Time to Biochemical Recurrence • Time to Metastatic disease • Patient Reported Outcomes	Active, not recruiting
Decipher NCT 02723734 240	Validation Study on the Impact of Decipher® Testing - VANDAAM Study (VANDAAM)	To determine whether a tumor test recently developed by GenomeDx Biosciences known as Decipher® can predict aggressive prostate cancer with the same accuracy in	Multisite, prospective validation Observational study 2 years	• Two-year PSA failure rate	Active, not recruiting

Test Trial Name (Short) Projected N	Full Trial Name	Objective	Study Design Follow-up	Outcomes Measured	Status/Projected Completion
		Black men (AAM) as in non-Black men (NAAM).			
Decipher NCT05050084 2050	Two Studies for Patients With Unfavorable Intermediate Risk Prostate Cancer Testing Less Intense Treatment for Patients With a Low Gene Risk Score and Testing a More Intense Treatment for Patients With a Higher Gene Risk Score	This phase III trial uses the Decipher risk score to guide intensification (for higher Decipher gene risk) or de-intensification (for low Decipher gene risk) of treatment to better match therapies to an individual patient's cancer aggressiveness.	Parallel Assignment Interventional 5 years	• Distant Metastasis (DM) • Metastasis-Free Survival (MFS) • Overall Survival • Time to PSA Failure • MFS including PET Imaging • Locoregional Failure • DM Including PET imaging • Prostate Cancer-specific mortality • Sexual and Hormonal Function related quality of life • Fatigue • Cognition • Locoregional Progression • Castrate-resistant prostate cancer • Bowel and Urinary Function related quality of life • Cardio-metabolic markers • PSA Failure-free survival with non-castrate testosterone and no additional therapies	Recruiting

Test Trial Name (Short) Projected N	Full Trial Name	Objective	Study Design Follow-up	Outcomes Measured	Status/Projected Completion
				• Locoregional failure based upon either conventional or molecular imaging • Health Utilities • Time to testosterone recovery	
Prolaris NCT04404894 500	Long-Term Prospective Registry in Prostate Cancer Patients From Diverse Urology Practice Settings Following Prolaris Testing	This registry will evaluate treatment selection for patients with newly diagnosed, localized prostate cancer following Prolaris testing. It will measure the proportion of men who initially select treatment with active surveillance, the time frame between active surveillance selection and any change in treatment, and clinical outcomes.	Prospective Observational 10 years	• Active Surveillance Durability; Comorbidities • Disease Progression • Baseline Clinicopathologic Measures • Proportion of men with prostate cancer who: (1) Meet NCCN hereditary high-risk criteria, (2) undergo and complete hereditary cancer genetic testing; and (3) are found to carry pathogenic variants in tested cancer-predisposition genes	Recruiting
All NCT04396808 900	Genomics in Michigan to Adjust Outcomes in Prostate cancer (G-MAJOR) for Men With Newly Diagnosed	To determine the clinical impact of Gene Expression Classifier (GEC) testing in prostate cancer care while also developing a pragmatic approach for improved GEC clinical use and future study.	Multisite Crossover Assignment Interventional 5 years	• Binomial proportion of men on active surveillance without treatment • Occurrence of grade reclassification • Rate of indolent pathology	Recruiting

Test Trial Name (Short) Projected N	Full Trial Name	Objective	Study Design Follow-up	Outcomes Measured	Status/Projected Completion
	Favorable Risk Prostate Cancer			• Mean score per arm of patient reported urinary function questionnaire • Proportion of patients with changes from baseline in urinary function exceeding minimal important differences • Mean score per arm of patient reported sexual function • Proportion of patients with changes from baseline in sexual function exceeding minimal important differences • Time to biochemical recurrence • Time to distant metastases • Mean score per arm of health-related quality of life • Rate of adverse pathology at prostatectomy • Rate of biochemical recurrence	
Prolaris NCT03290508	Long-term Study to Evaluate and Clinical Outcomes in	To determine whether Prolaris testing in patients with favorable intermediate risk prostate cancer influences physician	Prospective Observational 8 years	• Low Prolaris score, on active surveillance • Low Prolaris score, definitive treatment	Terminated (There are sufficient follow-up data to meet the endpoints of the study.)

Test Trial Name (Short) Projected N	Full Trial Name	Objective	Study Design Follow-up	Outcomes Measured	Status/Projected Completion
524	Patients with Favorable Intermediate Risk Localized Prostate Cancer	management decisions toward conservative treatment in patients with Prolaris low-risk scores without negatively impacting patient oncologic outcomes, thereby sparing low-risk patients from unnecessary treatments and associated side-effects.		following active surveillance • Low Prolaris score, disease progression following delayed definitive treatment • Low Prolaris score, time to definitive treatment • No Prolaris score, on active surveillance • No Prolaris score, definitive treatment following active surveillance • No Prolaris score, time to definitive treatment following active surveillance • No Prolaris score, disease progression following delayed definitive treatment	