Appendix 1. Search history for (a) PubMed/MEDLINE, (b) EMBASE, and (c) Cochrane Central.

a) PubMed

(((((("risk"[MeSH Terms] OR "risk"[All Fields]) AND stratification[All Fields]) OR ("risk assessment"[MeSH Terms] OR ("risk"[All Fields] AND "assessment"[All Fields]) OR "risk assessment"[All Fields]) OR ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields]) OR ("prognosis"[MeSH Terms] OR "prognosis"[All Fields]) OR ("risk"[MeSH Terms] OR "risk"[All Fields])) AND (("neoplasm staging"[MeSH Terms] OR ("neoplasm"[All Fields] AND "staging"[All Fields]) OR "neoplasm staging"[All Fields]) OR ("neoplasm grading"[MeSH Terms] OR ("neoplasm"[All Fields] AND "grading"[All Fields]) OR "neoplasm grading"[All Fields]) OR ("biological tumour markers"[All Fields] OR "tumor markers, biological"[MeSH Terms] OR ("tumor"[All Fields] AND "markers"[All Fields] AND "biological"[All Fields]) OR "biological tumor markers"[All Fields] OR ("biological"[All Fields] AND "tumor"[All Fields] AND "markers"[All Fields])) OR ("nomograms"[MeSH Terms] OR "nomograms"[All Fields]) OR ("prostate-specific antigen"[MeSH Terms] OR ("prostate-specific"[All Fields] AND "antigen"[All Fields]) OR "prostate-specific antigen"[All Fields] OR ("prostate"[All Fields] AND "specific"[All Fields] AND "antigen"[All Fields]) OR "prostate specific antigen"[All Fields]) OR ("polymorphism, single nucleotide"[MeSH Terms] OR ("polymorphism"[All Fields] AND "single"[All Fields] AND "nucleotide"[All Fields]) OR "single nucleotide polymorphism"[All Fields] OR ("single"[All Fields] AND "nucleotide"[All Fields] AND "polymorphism"[All Fields])) OR "SNP"[All Fields] OR "SNPs"[All Fields] OR PSA[All Fields] OR "prostate health index"[All Fields] OR PHI[All Fields] OR (4k[All Fields] AND score[All Fields]) OR "kallikrein panel"[All Fields] OR PCA3[All Fields] OR (TMPRSS2[All Fields] AND ERG[All Fields]) OR ERG[All Fields] OR TMPRSS2[All Fields] OR ("biological markers"[MeSH Terms] OR ("biological"[All Fields] AND "markers"[All Fields]) OR "biological markers"[All Fields] OR "biomarker"[All Fields]) OR ("biological markers"[MeSH Terms] OR ("biological"[All Fields] AND "markers"[All Fields]) OR "biological markers"[All Fields] OR "marker"[All Fields]) OR ("genetic testing"[MeSH Terms] OR ("genetic"[All Fields] AND "testing"[All Fields]) OR "genetic testing"[All Fields] OR ("genetic"[All Fields] AND "tests"[All Fields]) OR "genetic tests"[All Fields]) OR (("genomics"[MeSH Terms] OR "genomics"[All Fields] OR "genomic"[All Fields] OR "genome"[MeSH Terms] OR "genome"[All Fields]) AND tests[All Fields]) OR prolaris[All Fields] OR "cell cycle progression"[All Fields] OR "oncotype dx"[All Fields])) AND (("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "prostate cancer"[All Fields]) OR ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancers"[All Fields]) OR "prostate cancers"[All Fields]) OR ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostatic"[All Fields] AND "neoplasm"[All Fields]) OR "prostatic neoplasm"[All Fields]) OR ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields]))) AND (active surveillance[tiab] OR ("watchful waiting"[MeSH Terms] OR ("watchful"[All Fields] AND "waiting"[All Fields]) OR "watchful waiting"[All Fields]) OR observation[tiab] OR expectant management[tiab] OR ((insignificant[All Fields] OR indolent[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All

Fields])))

b) EMBASE:
(((prostate cancer or prostate cancer or prostate cancers or (prostatic neoplasm$ or prostate tumor)) and (risk assessment or risk assessment$ or risk stratification or risk factor or risk factor$ or risk or risk$ or (prognosis or cancer prognosis or prognosis)) and (watchful waiting or observation or (insignificant adj2 cancer) or (indolent adj2 cancer) or expectant management or watchful waiting or active surveillance) and (neoplasm staging or cancer staging or (neoplasm grading or cancer grading) or tumor marker or biological tumor marker$ or nomogram or nomogram$ or prostate specific antigen or prostate-specific antigen or single nucleotide polymorphism$ or single nucleotide polymorphism or SNP$ or PSA or PCA3 or kallikrein panel or 4k score or PHI or prostate health index or TMPRSS2:ERG or ERG or TMPRSS2 or biological marker or biomarker$ or marker$ or genetic test$ or genomic test$ or cell cycle progression or oncotype dx or prolaris or cell cycle progression or! genetic screening)) not (letter or editorial))

b) Cochrane Central:
'prostate cancer OR prostate cancers OR prostatic neoplasm OR prostatic neoplasms in Title, Abstract, Keywords and risk stratification OR risk assessment OR risk factors OR prognosis OR risk in Title, Abstract, Keywords and neoplasm staging OR neoplasm grading OR biological tumor markers OR nomograms OR prostate-specific antigen OR single nucleotide polymorphism OR "SNP" OR "SNPs" OR PSA OR "prostate health index" OR PHI OR "4k score" OR "kallikrein panel" OR PCA3 OR ERG OR TMPRSS2 OR biomarker OR marker OR genetic tests OR genomic tests OR prolaris OR "cell cycle progression" OR "oncotype dx" in Title, Abstract, Keywords and "active surveillance" OR watchful waiting OR "observation" OR "expectant management" OR ((insignificant OR indolent) AND cancer) in Title, Abstract, Keywords in Trials

Table

Appendix 2: Characteristics included studies

Authors and references	Yr of publication	Study design	Institution/ AS cohort	Population	Sample size
Tseng et al (5)	2010	Prospective	John Hopkins	Clinical stage T1c, PSA density ≤0.15 ng/ml/cm3, GS≤6, ≤2 biopsy cores with cancer, maximum of 50% involvement of any core with cancer	376
Abern et al (8)	2013	Retrospective	Duke Prostate Center Durham	PSA <10 ng/ml, GS≤ 6, and ≤ 33% of cores with cancer on diagnostic biopsy	145
Iremashvili et al (9)	2012	Prospective	University of Miami	GS<7, ≤2 positive biopsy cores, ≤20% tumor present in any core and clinical stage T1-T2a	249
Sundi et al (10)	2014	Prospective	Johns Hopkins	Clinical stage≤ T1, Gleason≤6, PSA<10, PSA density <0.15, positive cores <3, percent cancer per core ≤50%	654
Cohn et al (11)	2014	Prospective	University of Chicago	Clinical stage ≤ T2a, GS ≤6, ≤3 cores positive, maximum single core involvement <50%; total tumour volume ≤5% on diagnostic biopsy	165
Cullen et al (12)	2011	Retrospective	Center for Prostate Disease Research (CPDR) multicenter database	Men diagnosed with CaP between 1989 and 2008 initially on AS for a minimum of 9 months with at least 24 months of follow-up	690
Fleshner et al (13)	2011	Prospective	REDEEM trial	Clinical stage T1c-T2a PCa, GS ≤ 6, PSA ≤10 ng/mL. Entry biopsy of at least 10 cores had to be performed within 6 months of screening	289
Smith et al (14)	2009	Retrospective	Single institution	Low risk prostate cancer	71

Dall' Era et al (15)	2008	Prospective	UCSF	PSA <10 ng/mL, biopsy Gleason sum ≤ 6 with no pattern 4 or 5, cancer involvement of <33% of biopsy cores, and clinical stage T1/T2a tumor.	321
Patel et al (16)	2014	Prospective	Johns Hopkins	Stage T1c disease; PSAD<0.15; GS ≤ 6, ≤2 biopsy cores and 50% or less involvement of any core with cancer	275
Shappley et al (17)	2009	Prospective	Health Professionals Followup Study	Men diagnosed with PC between 1986 and 2007 who opted for deferred treatment (no treatment for at least 1 year after the date of PCa diagnosis)	342
Lin et al (18)	2013	Prospective	Canary Prostate Active Surveillance Study (PASS)	Histologically confirmed adenocarcinoma of the prostate, ECOG performance status of 0 or 1, clinical T1 and T2 disease, no previous treatment for PCa including hormonal therapy, radiotherapy surgery, or chemotherapy, and the willingness to undergo serial prostate biopsies	387
Bul et al (19)	2013	Prospective	ERSPC (PRIAS)	Clinical stage T1/T2 PCa, PSA≤ 10 ng/ml, PSAD <0.2 ng/ml per milliliter, 1 or 2 positive biopsy cores, and GS≤ 6	2494
Klotz et al (20)	2010	Prospective	University of Toronto	GS≤6, PSA≤10 ng/mL (less stringent for >70 initially)	450
Sternberg et al (21)	2014	Retrospective	MSKCC	cT1 or cT2a, PSA<10, GS≤6, ≤3 positive biopsy cores and ≤50% involvement of any single core	680
Whitson et al (22)	2011	Prospective	UCSF	PSA<10 ng/ml, clinical stage T1 or T2, GS≤6, 33% or fewer of at least 6 cores positive, no single core>50%	241
Zhang et al (23)	2006	Prospective	Sunnybrook, Toronto	T1b-T2b, GS ≤7, PSA ≤15	231
Berg et al (24)	2014	Prospective	University of Copenhagen	PSA≤10 ng/ml, clinical tumour stage ≤cT2a; GS ≤6; ≤3 cores with cancer; ≤50% tumor in any single core (except n=57 did not meet criteria)	265
Bul	2012	Prospecti	ERSPC	Clinical stage ≤ T2, PSA≤ 10 ng/ml, PSA density <0.2	757

et al (25)		ve	(PRIAS)	ng/ml per milliliter, 1 or 2 positive biopsy cores, GS≤ 6	
Cary et al (26)	2013	Prospecti ve	UCSF	PSA ≤10 ng/ml, clinical stage T1 or T2, biopsy GS 6, <33% positive cores, and <50% tumor in any single core	465
Egge ner et al (27)	2009	Retrospec tive	Multicent er study	Age ≤ 75, PSA <=10, GS ≤6, clinical stage T1-T2a, 3 or less positive biopsies, repeat biopsy before surveillance	262
Hira ma et al (28)	2014	Prospecti ve	Multi-institution al cohort (Japan)	stage T1cN0M0; age 50–80; PSA ≤ 20 ng/ml; 1 or 2 positive cores per 6–12 systematic biopsy cores; GS ≤6; maximum cancer involvement in positive cores of ≤50 %	67
Klot z et al (29)	2004	Prospecti ve	Universit y of Toronto	≤70 yr: GS≤6, PSA ≤10. >70 yr: GS ≤3+4, PSA<15	299
Mak arov et al (30)	2009	Prospecti ve	Johns Hopkins	Epstein criteria (T1c, PSAD ≤0.15, GS <7, <3 positive cores, ≤50% core involvement)	71
Solo way et al (31)	2008	Prospecti ve	Universit y of Miami	GS≤ 6, PSA ≤15 ng/mL, stage ≤T2, low-volume disease (≤50% of 2 biopsy cores) and >12 months of follow-up	99
Venk itara man et al (32)	2007	Prospecti ve	Royal Marsden Hospital	T1/2a, PSA < 15, GS ≤ 3+4, ≤50% positive cores	119
Corn u et al (33)	2013	Retrospec tive	PASS	Men either having biopsy for elevated PSA >3 (55% of population), or AS candidates undergoing restaging biopsy (T1c, GS <7, PSA <10, no ECE on MRI) (45% of population)	291
Ishar wal et al (34)	2010	Retrospec tive	Johns Hopkins	T1c, PSAD ≤0.15 ng/mL/cm3, GS<7, ≤2 cores involved with cancer, ≤50% of any core involved with cancer	71
van den Berg h et	2010	Prospecti ve	ERSPC (PRIAS)	Asymptomatic T1c/T2 PCa, PSA≤10.0 ng/mL, PSA density of <0.2 ng/mL/mL, GS≤3+3=6, 1 or 2 positive biopsy cores	500

al (35)					
San Francisco et al (36)	2011	Prospective	Multi-institutional cohort	Clinically localized disease (T1c-T2c), GS ≤6 with no pattern 4, <3 cores positive for cancer, ≤50% involvement in any core	120
Valeri et al (37)	2010	Retrospective	Multi-institutional cohort (France)	PSA<10, cTstage <T2b, GS <7, positive cores <3, length of PC/core <3 mm	60
Burton et al (38)	2012	Prospective	ProtecT trial	Clinical stage ≤T2 PCa, PSA<20 ng/mL (randomized to 3 trial arms: radical prostatectomy, radical radiotherapy, or active monitoring with regular PSA measurements)	404
Goh et al (39)	2013	Retrospective	Royal Marsden Hospital	Histologically confirmed PCa, stage T1/2a, N0, M0, Gleason score 3+3, PSA <15 ng/mL with cancer present in <50% of the total number of biopsy cores, ages 50-80, fit for radical treatment but chose AS for initial management. GS 3+4 only allowed if patients > 65 years	471
Mukerji et al (40)	2010	Retrospective	British cohort with low screening penetrance	T1c-T2a initially managed with AS	85
van den Bergh et al (41)	2009	Retrospective	ERSPC (PRIAS)	Screen-detected GS 7	50
Venkitaraman et al (42)	2008	Prospective	Royal Marsden Hospital	Clinical stage T1/T2a, N0/Nx, M0/Mx adenocarcinoma of the prostate with PSA<15 ng/mL, GS≤7 with primary grade ≤3, and less than half the biopsy cores positive	237
Jhavar et al (43)	2009	Prospective	Royal Marsden hospital	PSA <15, clinical stage T1/T2a, GS ≤3+4, <=50% positive cores	60

van As et al (44)	2008	Prospective	Royal Marsden Hospital	Clinical stage T1–T2a, N0–Nx, M0–Mx adenocarcinoma of the prostate with serum PSA < 15 ng/ml, Gleason score 7, primary Gleason grade ≤ 3, and % positive biopsy cores ≤ 50%.	326
Iremashvili et al (45)	2013	Prospective	University of Miami	GS<7, ≤2 positive biopsy cores, ≤20% tumor present in any core and clinical stage T1-T2a, PSA <15 with at least 2 surveillance biopsies	205
Iremashvili et al (46)	2013	Prospective	University of Miami	GS<7, ≤2 positive biopsy cores, ≤20% tumor present in any core, and clinical stage T1–T2a	161
Ng et al (47)	2008	Prospective	Royal Marsden Hospital	PSA <15, clinical stage T1/T2a, GS <=3+4, <=50% positive cores	199
Adamy et al (48)	2011	Retrospective	MSKCC	PSA<10 ng/ml, no GS 4 or 5, clinical stage T1–T2a, ≤3 positive biopsy cores (minimum 10), no biopsy core containing >50% cancer involvement and confirmatory biopsy to reassess eligibility before starting AS	238
Yee et al (49)	2010	Prospective	MSKCC	PSA < 10ng/ml, Gleason score 6 or less, cT2a or less, 3 or less positive cores and no more than 50% of a core involved by tumor.	297
Frommontet al (50)	2011	Prospective	Multi-institutional cohort	Age≤75 years, clinical stage T1c or T2a, Gleason ≤6, PSA<10 ng/ml, 2 (out of 12) or fewer biopsy cores with cancer, and each cancer foci 3 mm or less	155
Soloway et al (51)	2010	Prospective	University of Miami	GS≤6, PSA≤10, 1 or 2 positive cores with ≤20% tumor in each core	230
Umbehr et al (52)	2014	Prospective	Johns Hopkins	Clinical stage T1c, PSAD <0.15, GS 6, no Gleason pattern 4 or 5, 2 biopsy cores with cancer, maximum of 50% involvement of any core with cancer	640
Barayan et al (53)	2014	Retrospective	McGill University Health Center	<3 positive cores; GS ≤3+4; <50% of cancer on any involved biopsy core	155
Welt	2014	Retrospec	UCSF	PSA<10, <cT3, GS ≤6, <33% of bx cores positive,	764

y et al (54)		tive		<50% of any single biopsy core positive. Men who did not meet these criteria but still elected AS were followed as well	
Tosoian et al (55)	2012	Prospective	Johns Hopkins	Clinical stage T1c, PSA density <0.15 ng/ml/cm3, GS≤6, ≤2 biopsy cores with cancer, maximum of 50% involvement of any core with cancer	167
Komisarenko et al (56)	2014	Prospective	University of Toronto	GS 6	555
Loblaw et al (57)	2010	Prospective	University of Toronto	Stage T1b-T2b N0M0, GS≤7, PSA≤15 ng/ml	305
Kakehi (58)	2008	Prospective	Multi-institutional cohort (Japan)	Stage T1cN0M0, age 50–80, PSA≤20 ng/ml, 1 or 2 positive cores per 6–12 systematic biopsy cores, GS ≤6, cancer involvement in positive core ≤50%	118
Ross et al (59)	2010	Prospective	Johns Hopkins	PSA density < 0.15 ng/mL/cm(3), GS≤6 with no pattern ≥4, involving ≤2 cores with cancer, and ≤ 50% involvement of any core by cancer	290
Khatami et al (60)	2007	Prospective	ERSPC	The reasons for choosing AS were comorbidity, small-volume cancers in biopsies or patient's desire (or combination of these)). Small-volume cancers in biopsies were classified as 1 or 2 adjacent cores with a total core cancer length of less than 2 mm and where rebiopsies of the area did not reveal more cancer (mixed cohort with AS and WW)	270
Iremashvili et al (61)	2013	Prospective	University of Miami	GS<7, ≤2 positive biopsy cores, ≤20% tumor present in any core, and clinical stage T1-T2a	250
Krakowsky et al (62)	2010	Prospective	University of Toronto	PSA ≤10, GS ≤ 6 and T1c/T2a (Epstein criteria for men <55 years; for 1st 5 years also included 3+4=7 and PSA <15 for men >70 years)	453 (5 for further analysis)
Pujara et al	2010	Prospective	Cleveland Clinic	Low risk disease	99

(63)					
Tosoian et al (66)	2010	Prospective	Johns Hopkins	Clinical stage T1c, PSA density <0.15 ng/ml/cm3, GS≤6, ≤2 biopsy cores with cancer, maximum of 50% involvement of any core with cancer	294
Venkitaraman et al (67)	2008	Prospective	Royal Marsden Hospital	Patients with untreated, localised prostatic adenocarcinoma on a prospective clinical study of AS	191
Tausch et al (69)	2009	Prospective	CPDR	Men with very low and low risk disease	2058 (Including men who had surgery, radiation and AS)
van den Bergh et al (70)	2009	Prospective	ERSPC (PRIAS)	PRIAS	199

*ERSPC= European Randomized Study of Screening for PCa; UCSF=University of California, San Francisco; MSKCC=Memorial Sloan-Kettering Cancer Center

Appendix 3: Summary statistical significance of clinic-pathologic variables and biomarkers for risk stratification*

	Clinic-pathologic variables and biomarkers	Statistical significance
Patient factors		
	Race	Sig: (8-12) Not sig: (10, 13-18)
	Age	Sig: (12, 13, 17, 19-23) Not sig: (5, 8, 9, 14-18, 24-35)
	Family history	Sig: (13, 36, 37) Not sig: (9, 18, 33, 38, 39)
	BMI/ Metabolic syndrome	Sig: (11) Not sig: (9, 10, 17, 38)
Biopsy factors		
	Prostate volume	Sig: (9, 13, 22, 28) Not sig: (10, 27, 28, 30, 35, 44)
	Gleason score	Sig: (12, 15, 17, 20, 23, 38, 40, 41, 43) Not sig: (17, 24, 29, 31, 32, 42, 44)
	Extent of cancer on initial biopsy	Sig: (5, 9, 11, 14, 19, 21, 24, 25, 27, 32, 35, 40, 45-47) Not sig: (11, 24, 26, 28, 30, 34, 42, 44, 45, 48, 49)
	Restaging biopsy data	Sig: (26, 27, 45, 46, 48, 50, 51, 56)
PSA derivatives		
	PSA	Sig: (8, 13, 17-19, 21, 23, 29, 52) Not sig: (5, 9, 10, 14, 17, 20, 25, 27, 29-32, 34, 35, 42-44, 48, 55, 60)
	PSADT	Sig: (12, 19, 20, 23, 25, 29, 31, 47, 60) Not sig: (22, 35, 51, 58, 59, 61)
	PSAV	Sig: (14, 36, 47, 59, 61) Not sig: (13, 15, 16, 32)
	PSAV risk count	Sig: (16)
	PSA density	Sig: (5, 9, 11, 15, 19, 25, 26, 32, 33, 36, 42, 43, 45, 47, 53, 54) Not sig: (5, 16, 24, 30, 34, 44, 48)
	%fPSA	Sig: (5, 29, 44, 55) Not sig: (5, 30, 34, 60)
	%-2proPSA/ phi	Sig: (28, 30, 34, 36)
Genetics/ genomics and other factors		
	Urinary PCA3 and TMPRSS2:ERG	Sig: (33) Not sig: (18, 66)
	ERG in tissue	Sig: (24)
	DNA content	Sig: (34)

	Ki-67	Sig: (43)
	Urinary phytoestrogens	Not sig: (67)
	SNPs	Not sig: (33, 39)

*Endpoints of evaluated studies ranged from PSA kinetics to reclassification by volume and/or grade on repeat biopsy, time to treatment, and mortality. Some studies evaluated multiple endpoints so may be included multiple times.