Table S1. Example of the original/reverse coding direction of inheritance mode on recessive-dominant SNP-SNP interaction models using the two SNPs (rs2075110-rs7538029) associated with prostate cancer aggressiveness (n=21,314)

rs2075110-rs7538029	Coding direction[1] p-value of the interaction			
Model type	Original-original (oo)	Reverse-original (ro)	Original-reverse (or)	Reverse-reverse (rr)
RD_Full	**0.011**	0.011	0.011	0.011
RD_M1_int	**0.526**	**$3.5x10^{-5}$**	0.526	$3.5x10^{-5}$
RD_M2_int	**0.247**	0.247	**0.008**	0.008
RD_int	**0.829**	**0.0007**	**0.155**	**$2.6x10^{-5}$**

[1]original mode is based on the minor allele. Unique p-values in each model type are bold.

Table S2. Power comparisons of SIPI and other four statistical approaches[1] in detecting SNP-SNP interactions for Models 1-3

Model 1[2]	P(outcome)=(0.30,0.30,0.20,0.30,0.30,0.20,0.20,0.20,0.20)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.537	0.493	0.493	0.280	0.103	0.102	0.007	1.000	0.998	0.998	0.997	0.946	0.938	0.014
MDR	0.497	0.502	0.627	0.170	0.109	0.122	0.050	0.998	1	0.999	0.838	0.595	0.594	0.067
AA_Full	0.052	0.057	0.036	0.044	0.044	0.040	0.040	0.144	0.088	0.037	0.078	0.044	0.031	0.043
Geno_Full	0.085	0.081	0.046	0.071	0.062	0.049	0.055	0.134	0.271	0.143	0.078	0.074	0.053	0.046
SNPassoc	0.071	0.056	0.023	0.048	0.048	0.027	0.022	0.201	0.100	0.040	0.119	0.042	0.040	0.024
Model 2[2]	P(outcome)=(0.20,0.20,0.20,0.20,0.30,0.30,0.20,0.30,0.30)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.654	0.579	0.160	0.554	0.224	0.096	0.037	0.998	0.996	0.872	1.000	0.952	0.722	0.242
MDR	0.651	0.586	0.105	0.498	0.192	0.077	0.077	1	0.997	0.563	0.995	0.701	0.276	0.107
AA_Full	0.161	0.187	0.089	0.280	0.231	0.144	0.125	0.663	0.662	0.352	0.888	0.812	0.559	0.480
Geno_Full	0.181	0.224	0.107	0.292	0.202	0.139	0.161	0.759	0.755	0.399	0.911	0.739	0.520	0.383
SNPassoc	0.150	0.188	0.074	0.283	0.177	0.107	0.071	0.713	0.706	0.317	0.923	0.777	0.500	0.324
Model 3[2]	P(outcome) [1]=(0.30,0.20,0.20,0.30,0.20,0.20,0.20,0.20,0.20)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.643	0.659	0.577	0.699	0.454	0.265	0.108	0.998	0.999	1.000	0.995	0.998	1.000	0.950
MDR	0.651	0.698	0.667	0.78	0.494	0.268	0.243	0.999	1	1	1	1	0.964	0.906
AA_Full	0.200	0.211	0.080	0.100	0.084	0.066	0.042	0.698	0.667	0.317	0.286	0.213	0.120	0.050
Geno_Full	0.186	0.187	0.092	0.120	0.092	0.065	0.080	0.756	0.697	0.343	0.382	0.228	0.146	0.069
SNPassoc	0.170	0.170	0.057	0.074	0.073	0.043	0.030	0.740	0.687	0.278	0.252	0.144	0.099	0.027

[1]SIPI: SNP Interaction Pattern Identifier; MDR: Multifactor Dimensionality Reduction (test an overall association allowing an interaction); AA_Full and Geno_Full: full interaction logistic model with additive and genotypic SNPs, respectively, and SNPassoc: SNP interaction approach in SNPassoc R package

[2]Percentages of the outcome event in the nine genotype combinations (TL, TM, TR, ML, MM, MR, BL, BM, BR). T: top, M: middle, B: bottom, L: left, R: right; MAF=minor allele frequency

Table S3. Power comparisons of SIPI and other four statistical approaches[1] in detecting SNP-SNP interactions for Models 4-6

Model 4[2]	P(outcome)= (0.20,0.20,0.20,0.30,0.40,0.40,0.30,0.40,0.40)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.726	0.744	0.594	0.612	0.811	0.781	0.563	1.000	0.999	0.918	0.984	0.929	0.880	0.909
MDR	0.928	0.862	0.685	0.986	0.942	0.903	0.757	1	1	1	1	1	1	1
AA_Full	0.117	0.141	0.068	0.235	0.173	0.110	0.121	0.513	0.527	0.260	0.786	0.667	0.432	0.391
Geno_Full	0.148	0.169	0.089	0.221	0.158	0.127	0.123	0.602	0.583	0.266	0.773	0.573	0.376	0.319
SNPassoc	0.126	0.144	0.069	0.223	0.132	0.074	0.054	0.546	0.525	0.216	0.831	0.625	0.357	0.253
Model 5[2]	P(outcome)= (0.08,0.13,0.21,0.13,0.33,0.62,0.21,0.62,0.91)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.760	0.774	0.986	0.727	0.911	0.952	0.784	1.000	1.000	0.794	1.000	0.951	0.730	0.793
MDR	1	1	0.982	1	0.989	0.938	0.685	1	1	1	1	1	1	1
AA_Full	0.915	0.831	0.437	0.877	0.595	0.367	0.203	1.000	1.000	0.984	1.000	1.000	0.963	0.732
Geno_Full	0.755	0.656	0.333	0.718	0.423	0.288	0.196	1.000	1.000	0.928	1.000	0.988	0.883	0.603
SNPassoc	0.801	0.709	0.285	0.742	0.404	0.223	0.105	1.000	1.000	0.932	1.000	0.990	0.887	0.556
Model 6[2]	P(outcome)= (0.18,0.18,0.18,0.18,0.18,0.18,0.18,0.29,0.29)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.397	0.290	0.055	0.124	0.047	0.013	0.006	0.999	0.988	0.456	0.799	0.321	0.113	0.010
MDR	0.267	0.183	0.07	0.088	0.065	0.045	0.056	0.884	0.644	0.124	0.211	0.079	0.073	0.044
AA_Full	0.254	0.271	0.125	0.128	0.109	0.084	0.046	0.842	0.833	0.520	0.406	0.348	0.203	0.055
Geno_Full	0.234	0.263	0.132	0.142	0.111	0.088	0.075	0.883	0.864	0.499	0.514	0.380	0.242	0.073
SNPassoc	0.211	0.233	0.082	0.101	0.060	0.045	0.027	0.871	0.845	0.476	0.360	0.262	0.143	0.025

[1]SIPI: SNP Interaction Pattern Identifier; MDR: Multifactor Dimensionality Reduction (test an overall association allowing an interaction); AA_Full and Geno_Full: full interaction logistic model with additive and genotypic SNPs, respectively, and SNPassoc: SNP interaction approach in SNPassoc R package

[2]Percentages of the outcome event in the nine genotype combinations (TL, TM, TR, ML, MM, MR, BL, BM, BR). T: top, M: middle, B: bottom, L: left, R: right; MAF=minor allele frequency

Table S4. Comparisons of type I errors of SIPI and other four statistical approaches[1] in detecting SNP-SNP interactions in the null model

Null Model[2]	P(outcome)= (0.2,0.2, 0.2,0.2,0.2,0.2,0.2,0.2,0.2,0.2)													
sample size	1000							5000						
MAF (SNP1, SNP2)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)	(0.5,0.3)	(0.5,0.2)	(0.5,0.05)	(0.3,0.3)	(0.3,0.1)	(0.3,0.05)	(0.1,0.05)
SIPI	0.017	0.017	0.006	0.013	0.007	0.004	0.005	0.015	0.017	0.011	0.021	0.010	0.009	0.011
MDR	0.056	0.056	0.045	0.053	0.055	0.052	0.055	0.031	0.045	0.053	0.06	0.051	0.068	0.047
AA_Full	0.051	0.061	0.048	0.043	0.048	0.041	0.038	0.047	0.056	0.044	0.042	0.042	0.048	0.034
Geno_Full	0.046	0.063	0.042	0.064	0.051	0.043	0.061	0.054	0.066	0.061	0.053	0.064	0.054	0.052
SNPassoc	0.046	0.057	0.041	0.043	0.029	0.025	0.026	0.035	0.043	0.040	0.029	0.033	0.037	0.021

[1]SIPI: SNP Interaction Pattern Identifier; MDR: Multifactor Dimensionality Reduction (test an overall association allowing an interaction); AA_Full and Geno_Full: full interaction logistic model with additive and genotypic SNPs, respectively, and SNPassoc: SNP interaction approach in SNPassoc R package

[2]Percentages of the outcome event in the nine genotype combinations (TL, TM, TR, ML, MM, MR, BL, BM, BR). T: top, M: middle, B: bottom, L: left, R: right; MAF=minor allele frequency

Table S5. Main effect tests and minor allele frequency (MAF) of the eight SNPs with a promising interaction associated with prostate cancer aggressiveness in the PRACTICAL study

					Combined set		
SNP	Minor<Major allele	Discovery MAF	Validation MAF	Combined MAF	Best Mode[1]	OR (95% CI)[2]	p-value
rs10488141	T<A	0.196	0.198	0.197	Rec	1.14 (0.96-1.36)	0.145
rs6994019	A<C	0.253	0.255	0.254	Dom	0.98 (0.92-1.06)	0.659
rs2058502	A<G	0.498	0.501*	0.499	Dom	1.10 (1.02-1.20)	0.020
rs4947972	C<G	0.278	0.275	0.276	Rec	1.13 (1.00-1.29)	0.058
rs723527	G<A	0.432	0.433	0.432	Rec	1.14 (1.04-1.24)	0.004
rs845555	A<G	0.464	0.453	0.458	Add	1.05 (1.00-1.10)	0.048
rs2075110	G<A	0.476	0.478	0.477	Rec	1.06 (0.97-1.15)	0.183
rs7538029	A<C	0.211	0.207	0.209	Add	1.11 (1.05-1.18)	0.0004

*G allele became a minor allele in the validation set

[1] Mode with the smallest p-value

[2] Odds ratio (95% confidence interval)

Figure S1. Nine models of SNP1 and SNP2 with the dominant-dominant mode (part1)

Model structure Model label (details)[1]	Number of sub-groups	Interaction patterns $logit(Y)_i = \beta_0 + \beta_1 SNP_{1i} + \beta_2 SNP_{2i} + \beta_3 SNP_{1i} \times SNP_{2i} + \epsilon_i$	Note
Full interaction DD_Full (dSNP1, dSNP2, dSNP1xdSNP2)	4	SNP_2 / SNP_1: Log(odds) BB (0) Bb/bb (1) AA (0): β_0 ; $\beta_0+\beta_2$ Aa/aa (1): $\beta_0+\beta_1$; $\beta_0+\beta_1+\beta_2+\beta_3$	Significant test of interaction has the same results regardless the original or reverse coding of the inheritance mode
Main1+int DD_M1_int_o_1 (dSNP1, dSNP1*dSNP2)	3	SNP_2 / SNP_1: Log(odds) BB (0) Bb/bb (1) AA (0): β_0 ; β_0 Aa/aa (1): $\beta_0+\beta_1$; $\beta_0+\beta_1+\beta_3$	The original or reverse coding only matters for the SNP with an main effect in this model
DD_M1_int_r_1 (rdSNP1, rdSNP1*dSNP2)		SNP_2 / SNP_1: Log(odds) BB (0) Bb/bb (1) AA (1): $\beta_0+\beta_1$; $\beta_0+\beta_1+\beta_3$ Aa/aa (0): β_0 ; β_0	
Main2+int DD_M2_int_o_2 (dSNP2, dSNP1*dSNP2)	3	SNP_2 / SNP_1: Log(odds) BB (0) Bb/bb (1) AA (0): β_0 ; $\beta_0+\beta_2$ Aa/aa (1): β_0 ; $\beta_0+\beta_2+\beta_3$	The original or reverse coding only matters for the SNP with an main effect in this model
DD_M2_int_r_2 (rdSNP2, dSNP1*rdSNP2)		SNP_2 / SNP_1: Log(odds) BB (1) Bb/bb (0) AA (0): $\beta_0+\beta_2$; β_0 Aa/aa (1): $\beta_0+\beta_2+\beta_3$; β_0	

[1]dSNP1 denote a dominant mode of SNP1 based on the minor allele, rdSNP1 denotes SNP1 with a reverse dominant mode

Figure S2. Nine models of SNP1 and SNP2 with the dominant-dominant mode (part 2)

Model structure unique model[1]	Number of sub-groups	Interaction patterns $logit(Y)_i = \beta_0 + \beta_1 \mathrm{SNP}_{1i} + \beta_2 \mathrm{SNP}_{2i} + \beta_3 \mathrm{SNP}_{1i} \times \mathrm{SNP}_{2i} + \epsilon_i$	Note
Int-only DD_int_oo (dSNP1*dSNP2)	2	SNP_1 \ SNP_2: BB (0) / Bb/bb (1) AA (0): β_0 / β_0 Aa/aa (1): β_0 / $\beta_0+\beta_3$	the original or reverse coding of both SNPs matter for the interaction significance test
DD_int_ro (rdSNP1*dSNP2)		SNP_1 \ SNP_2: BB (0) / Bb/bb (1) AA (1): β_0 / $\beta_0+\beta_3$ Aa/aa (0): β_0 / β_0	
DD_int_or (dSNP1*rdSNP2)		SNP_1 \ SNP_2: BB (1) / Bb/bb (0) AA (0): β_0 / β_0 Aa/aa (1): $\beta_0+\beta_3$ / β_0	
DD_int_rr (rdSNP1*rdSNP2)		SNP_1 \ SNP_2: BB (1) / Bb/bb (0) AA (1): $\beta_0+\beta_3$ / β_0 Aa/aa (0): β_0 / β_0	

[1]dSNP1 denote a dominant mode of SNP1 based on the minor allele, rdSNP1 denotes SNP1 with a reverse dominant mode

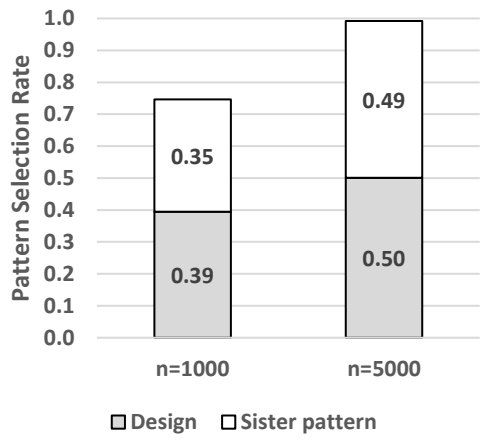
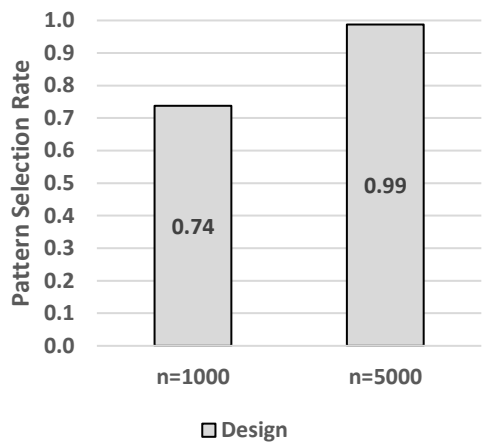
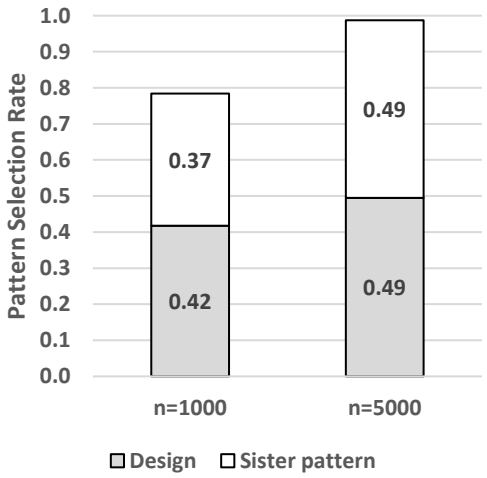
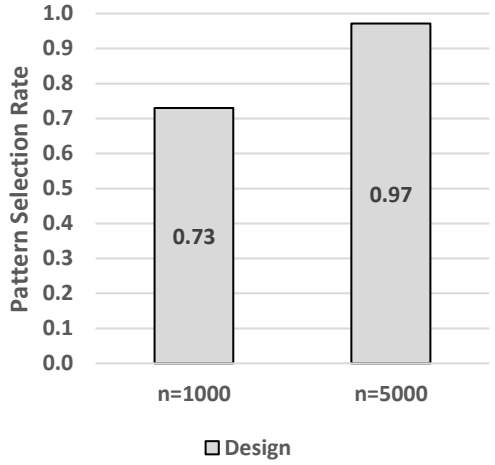
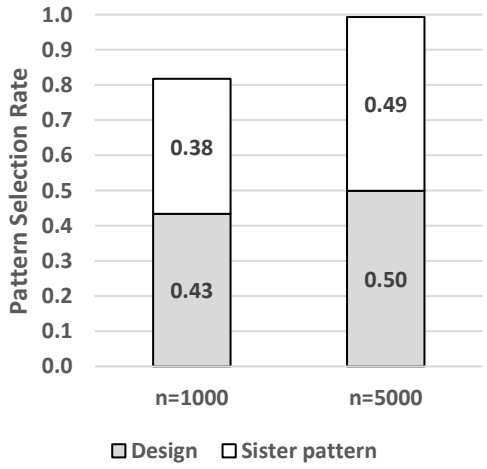
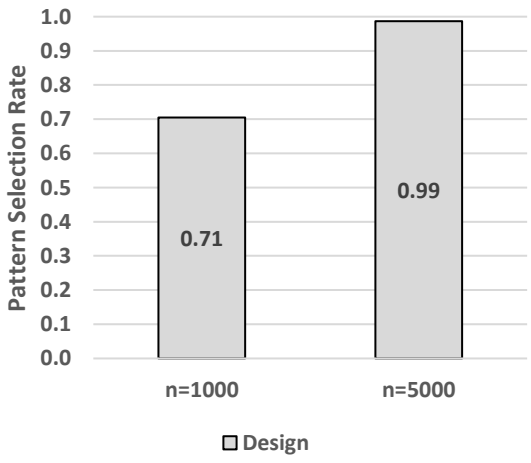
Figure S3. Interpretation of the designed and sister pattern[1] in the SNP Interaction Pattern Identifier (SIPI) for a SNP with a minor allele frequency (MAF) close to 0.5

SNP1 (A<G)[2], SNP2 (C<G) Designed pattern: DD_int_rr	SNP1 (G<A)[2], SNP2 (C<G) Sister pattern: RD_int_or
SNP1\ SNP2 GG CG CC **GG** Low risk AG AA	**SNP1\ SNP2** GG CG CC **AA** AG GG Low risk

[1] The 3x3 table is with the homozygous major genotypes on the left top corner in SIPI. The correct pattern is (GG+ GG) as the low-risk group.

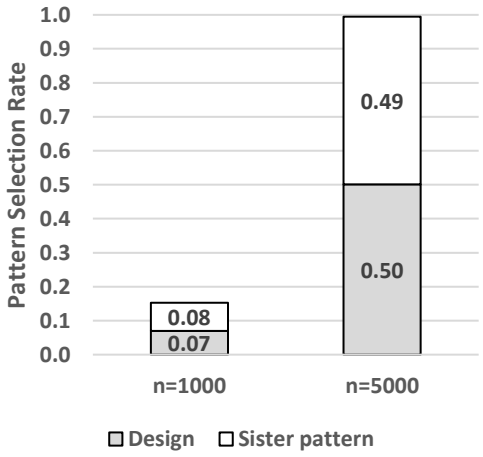
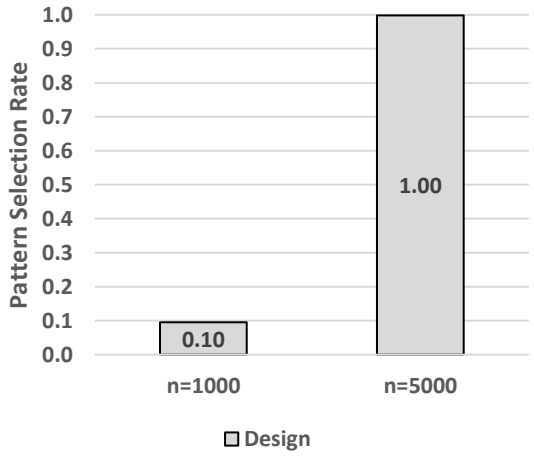
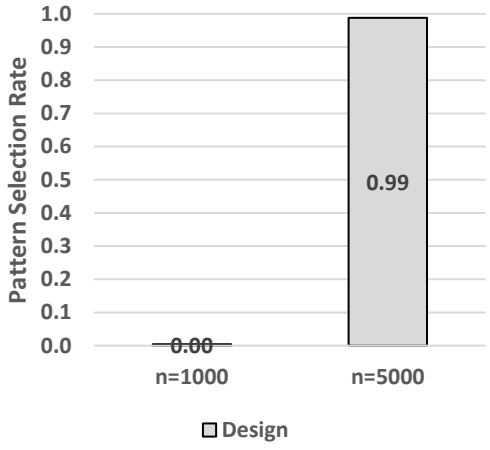
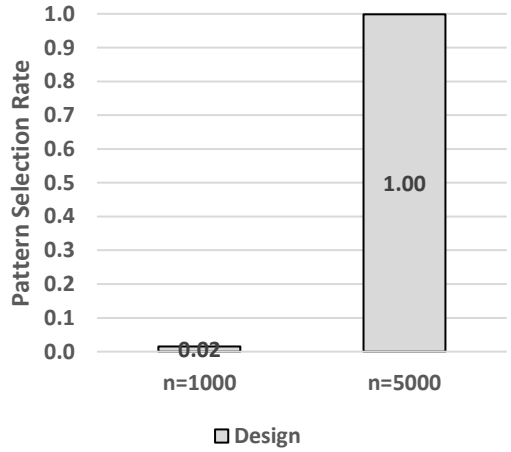
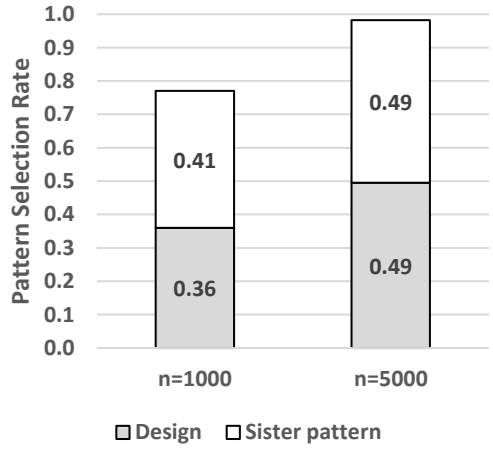
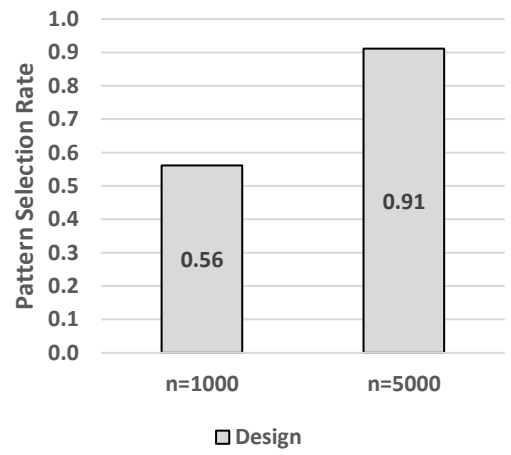
[2] (A<G) means "G" is the major allele and "A" is the minor allele. When SNP1 MAF~0.5, half of the simulation runs treated "G" as the major allele, and the other half treated "A" as the major allele.

Figure S4. Pattern identification rate by minor allele conditions for Models 1-3

Model Design (sister)[a] Pattern	SNP1 and SNP2 MAF=(0.5, 0.3)	SNP1 and SNP2 MAF=(0.3, 0.3)
Model 1 RR_int_rr (DR_int_or)		
Model 2 DD_int_oo (RD_int_ro)		
Model 3 RD_int_rr (DD_int_or)		

[a] Sister pattern is only for a SNP pair with a MAF=(0.5, 0.3)

Figure S5. Pattern identification rate by minor allele conditions for Models 4-6

Model Design (sister)[a] Pattern	SNP1 and SNP2 MAF=(0.5, 0.3)	SNP1 and SNP2 MAF=(0.3, 0. 3)
Model 4 DD_M1_int_o_1 (RD_M1_int_r_1)		
Model 5 AA_Full		
Model 8 RD_int_oo (DD_int_ro)		

[a] Sister pattern is only for a SNP pair with a MAF=(0.5, 0.3)

PRACTICAL Consortium:
Information of the PRACTICAL consortium can be found at http://practical.ccge.medschl.cam.ac.uk/.

Additional members from the consortium are: Margaret Cook [1], Angela Morgan [2], Artitaya Lophatananon [3,4], Cyril Fisher [2], Daniel Leongamornlert [2], Edward J. Saunders [2], Emma J. Sawyer [2], Koveela Govindasami [2], Malgorzata Tymrakiewicz [2], Michelle Guy [2], Naomi Livni [2], Rosemary Wilkinson [2], Sara Jugurnauth-Little [2], Steve Hazel [2], Tokhir Dadaev [2], Melissa C. Southey [5], Liesel M. Fitzgerald [6], John Pedersen [7], John Hopper [8], Robert MacInnis [6,8], Robert Szulkin [9], Ami Karlsson [9], Carin Cavalli-Bjoerkman [9], Jan-Erik Johansson [9], Jan Adolfson [9], Markus Aly [9,10], Michael Broms [9], Paer Stattin [9], Brian E. Henderson [11], Fredrick Schumacher [51], Anssi Auvinen [12], Kimmo Taari [13], Liisa Maeaettaenen [14], Paula Kujala [15], Teemu Murtola [16,17], Teuvo LJ Tammela [17], Csilla Sipeky [18], Andreas Roder [19], Peter Iversen [19], Peter Klarskov [20], Sune F. Nielsen [21,22], Tim J. Key [23], Hans Wallinder [24], Sven Gustafsson [24], Jenny L. Donovan [25], Freddie Hamdy [26], Angela Cox [27], Anne George [28], Athene Lane [28], Gemma Marsden [26], Michael Davis [25], Paul Brown [25], Paul Pharoah [29], Lisa B. Signorello [31,30], Wei Zheng [32], Shannon K. McDonnell [33], Daniel J. Schaid [33], Liang Wang [33], Lori Tillmans [33], Shaun Riska [33], Antje Rinckleb [34], Kathleen Herkommer [35], Manuel Luedeke [34], Walther Vogel [36], Dominika Wokolorczyk [37], Jan Lubiski [37], Wojciech Kluzniak [37], Kai-Uwe Saum [39], Christa Stegmaier [40], Babu Zachariah [41], Hyun Park [41], James Haley [41], Maria Rincon [41], Selina Radlein [41], Chavdar Slavov [42], Aleksandrina Vlahova [43], Atanaska Mitkova [44], Darina Kachakova [44], Elenko Popov [42], Svetlana Christova [43], Tihomir Dikov [43], Vanio Mitev [44], Allison Eckert [45], APCB BioResource [45,46], Amanda Spurdle [47], Angus Collins [45], Glenn Wood [45], Greg Malone [45], Judith A. Clements [45], Kimberly Alexander [45], Kris Kerr [45], Mary-Anne Kedda [45], Megan Turner [45], Pamela Saunders [45], Peter Heathcote [45], Srilakshmi Srinivasan [45], Tracy Omara [45], Trina Yeadon [45], Joana Santos [48], Carmen Jerónimo[48], Paula Paulo [48], Pedro Pinto [48], Rui Henrique [48], Sofia Maia [48], Agnieszka Michael [49], Andrzej Kierzek [49], Huihai Wu [49], Suzanne Kolb[50], Hong-Wei Zhang[52].

[1] Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK, [2] The Institute of Cancer Research, Sutton, UK, [3] Institute of Population Health, University of Manchester, Manchester, UK, [4] Warwick Medical School, University of Warwick, Coventry, UK, [5] Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia, [6] Cancer Epidemiology Centre, The Cancer Council Victoria, 615 St Kilda Road, Melbourne, Victoria, Australia, [7] Tissupath Pty Ltd., Melbourne,Victoria 3122, Australia, [8] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia, [9] Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, [10] Department of Clinical Sciences at Danderyds Hospital, Stockholm, Sweden, [11] Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California, USA, [12] Department of Epidemiology, School of Health Sciences, University of Tampere, Tampere, Finland, [13] Department of Urology, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland, [14] Finnish Cancer Registry, Helsinki, Finland, [15] Fimlab Laboratories, Tampere University Hospital, Tampere, Finland, [16] School of Medicine, University of Tampere, Tampere, Finland, [17] Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Finland, [18] Department of Medical Biochemistry and Genetics, Institute of Biomedicine, Kiinamyllynkatu 10, FI-20014 University of Turku, Finland, [19] Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, Copenhagen University Hospital, Tagensvej 20, 7521, DK-2200 Copenhagen, Denmark, [20] Department of Urology, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-230 Herlev, Denmark, [21] Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-230 Herlev, Denmark, [22] Faculty of Health and Medical Sciences, University of Copenhagen, [23] Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK, [24] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK, [25] School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK, [26] Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK, [27] CR-UK/YCR Sheffield Cancer Research Centre, University of Sheffield, Sheffield, UK, [28] University of Cambridge, Department of Oncology, Box 279, Addenbrooke's Hospital, Hills Road Cambridge CB2 0QQ, UK, [29] Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, UK, [30]

International Epidemiology Institute, 1555 Research Blvd., Suite 550, Rockville, MD 20850, USA, [31] Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA, [32] Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 800, Nashville, TN 37232 USA, [33] Mayo Clinic, Rochester, Minnesota, USA, [34] Department of Urology, University Hospital Ulm, Germany, [35] Department of Urology, Klinikum rechts der Isar der Technischen Universitaet Muenchen, Munich, Germany, [36] Institute of Human Genetics, University Hospital Ulm, Germany, [37] International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, [39] Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany, [40] Saarland Cancer Registry, 66119 Saarbruecken, Germany, [41] Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA, [42] Department of Urology and Alexandrovska University Hospital, Medical University, Sofia, Bulgaria, [43] Department of General and Clinical Pathology, Medical University, Sofia, Bulgaria, [44] Department of Medical Chemistry and Biochemistry, Molecular Medicine Center, Medical University, Sofia, 2 Zdrave Str., 1431 Sofia, Bulgaria, [45] Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Science, Queensland University of Technology, Brisbane, Australia, [46] Australian Prostate Cancer BioResource, Brisbane, QLD, [47] Molecular Cancer Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Australia, [48] Department of Genetics, Portuguese Oncology Institute, Porto, Portugal, [49] The University of Surrey, Guildford, Surrey, GU2 7XH, UK, [50] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, 98109-1024, USA, [51] Case Western Reserve University, School of Medicine, 10900 Euclid Ave., Cleveland, OH, 44106-4945, USA, [52] Second Military Medical University, 800 Xiangyin Rd., Shanghai 200433, P. R. China.

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