Supplementary material

Lakeman et al. Addition of a 161-SNP Polygenic Risk Score to family history-based risk prediction: impact on clinical management in non-*BRCA1/2* breast cancer families.

Lakeman IMM, *et al. J Med Genet* 2019; 0:581–589. doi: 10.1136/jmedgenet-2019-106072

Methods

Quality Control

For the ORIGO cohort quality control was performed as part of association studies conducted by the Breast Cancer Association Consortium (BCAC)[1 2]. To summarise the thresholds used, individuals were excluded when they were genotypically not female, overall call-rate was <95%, low or high heterozygosity ($P<1x10^{-6}$), first-degree relatives determined by identity-by-state estimates or in the case of ancestry outliers by multidimensional scaling. SNPs were excluded with call rates <95% or deviation from Hardy-Weinberg equilibrium in controls at $P<1x10^{-7}$.

For the family-based cohort, quality control was performed with Plink version 1.7[3 4], which excluded 14342 SNPs with a call rate below 98%. For the remaining SNPs, there was no deviation from Hardy-Weinberg equilibrium in controls at $P<1x10^{-3}$. In total 27 individuals were excluded of which 19 individuals with a call rate below 96% and 6 individuals because of another degree of relatedness than expected based on identity-by-state estimates and pedigree information. Two individuals were genotypically not female and were excluded from further analysis.

Multidimensional scaling was performed to determine clustering of families, including the Hungarian families. There were no different clusters for families, therefore we could also include the Hungarian families.

Lakeman IMM, *et al. J Med Genet* 2019; 0:581–589. doi: 10.1136/jmedgenet-2019-106072

Supplementary Tables

Table S1: 161 breast cancer associated SNPs used for calculating the Polygenic Risk Score[2]

Location	Variant	Chr	Position*	Alleles	MAF	OR (95%CI)[2]	P-value[2]	Genes
1p36.22	rs616488	1	10566215	A/G	0.33	0.94(0.93-0.96)	5.0X10-20	PEX14
1p36.13	rs2992756	1	18807339	C/T	0.49	1.06(1.04-1.08)	1.6x10-15	KLHDC7A
1p34.2	rs4233486	1	41380440	T/C	0.36	0.97(0.95-0.98)	9.1x10-09	-
1p34.2	rs79724016	1	42137311	T/G	0.03	0.93(0.88-0.97)	3.5x10-08	HIVEP3
1p34.1	rs1707302	1	46600917	G/A	0.34	0.96(0.95-0.98)	3.0x10-08	PIK3R3, LOC101929626
1p32.3	rs140850326	1	50846032	I/D9	0.49	0.97(0.95-0.99)	3.9x10-08	-
1p22.3	rs17426269	1	88156923	G/A	0.15	1.05(1.02-1.07)	1.7x10-08	-
1p13.2	rs11552449	1	114448389	C/T	0.17	1.04(1.01-1.06)	4.6X10-11	DCLRE1B
1p12	rs7529522	1	118230221	T/C	0.23	1.06(1.04-1.08)	1.7x10-10	-
1p11.2	rs11249433	1	121280613	A/G	0.41	1.11(1.09-1.13)	1.8X10-52	EMBP1
1q21.1	rs12405132	1	145644984	C/T	0.37	0.97(0.95-0.99)	6.3X10-10	RNF115
1q21.2	rs12048493	1	149927034	A/C	0.38	1.04(1.02-1.06)	8.6X10-14	OTUD7B
1q22	rs4971059	1	155148781	G/A	0.35	1.05(1.03-1.07)	4.8x10-11	TRIM46
1q32.1	rs35383942	1	201437832	C/T	0.06	1.12(1.08-1.17)	3.8x10-13	PHLDA3
1q41	rs11117758	1	217220574	G/A	0.21	0.95(0.93-0.97)	3.9x10-09	ESRRG
1q43	rs72755295	1	242034263	A/G	0.03	1.15(1.09-1.2)	1.7X10-14	EXO1
2p25.1	rs113577745	2	10135681	C/G	0.1	1.08(1.05-1.11)	3.9x10-10	GRHL1
2p24.1	rs12710696	2	19320803	C/T	0.37	1.03(1.01-1.04)	1.3X10-08	-
2p23.3	rs6725517	2	25129473	A/G	0.41	0.96(0.94-0.98)	2.9x10-12	ADCY3
2q13	rs71801447	2	111925731	CTTATGTT/C	0.06	1.09(1.05-1.13)	3.7x10-08	BCL2L11
2q14.1	rs4849887	2	121245122	C/T	0.1	0.91(0.88-0.94)	6.9X10-20	
2q31.1	rs2016394	2	172972971	G/A	0.47	0.95(0.94-0.97)	6.2X10-12	DLX2-AS1
2q31.1	rs1550623	2	174212894	A/G	0.15	0.95(0.93-0.98)	5.4X10-10	CDCA7

Lakeman IMM, *et al. J Med Genet* 2019; 0:581–589. doi: 10.1136/jmedgenet-2019-106072

2q33.1	rs1830298	2	202181247	T/C	0.28	1.06(1.04-1.08)	1.9X10-16	CASP8/ALS2CR12
2q35	rs4442975	2	217920769	G/T	0.5	0.89(0.87-0.9)	1.1X10-95	IGFBP5
2q35	rs34005590	2	217963060	C/A	0.05	0.82(0.79-0.86)	3.2X10-41	IGFBP5
2q35	rs16857609	2	218296508	C/T	0.26	1.06(1.04-1.09)	1.8X10-25	DIRC3
2q36.3	rs12479355	2	227226952	A/G	0.21	0.96(0.94-0.98)	2.4x10-08	-
3p26.1	rs6762644	3	4742276	A/G	0.38	1.05(1.03-1.07)	4.0X10-18	EGOT/ITPR1
3p24.1	rs4973768	3	27416013	C/T	0.47	1.11(1.09-1.13)	4.8X10-57	SLC4A7
3p.24.1	rs12493607	3	30682939	G/C	0.34	1.05(1.03-1.07)	6.9X10-14	TGFBR2
3p21.31	rs6796502	3	46866866	G/A	0.1	0.92(0.89-0.95)	5.5X10-15	
3p14.1	rs1053338	3	63967900	A/G	0.14	1.05(1.02-1.07)	5.3X10-11	ATNX7
3p13	rs6805189	3	71532113	T/C	0.48	0.97(0.95-0.99)	4.6x10-08	FOXP1
3p12.1	rs13066793	3	87037543	A/G	0.09	0.94(0.91-0.97)	1.0x10-09	VGLL3
3p12.1	rs9833888	3	99723580	G/T	0.22	1.06(1.04-1.08)	5.2x10-10	CMSS1, FILIP1L
3q23	rs34207738	3	141112859	CTT/C	0.41	1.06(1.04-1.08)	3.2x10-15	ZBTB38
3q26.31	rs58058861	3	172285237	G/A	0.21	1.06(1.04-1.09)	1.9x10-10	-
4p14	rs6815814	4	38816338	A/C	0.26	1.06(1.04-1.08)	6.1x10-13	-
4q21.23	4:84370124	4	84370124	TA/TAA	0.47	1.04(1.02-1.05)	2.2x10-09	HELQ
4q22.1	rs10022462	4	89243818	C/T	0.44	1.04(1.02-1.06)	1.6x10-09	LOC105369192
4q24	rs9790517	4	106084778	C/T	0.23	1.04(1.01-1.06)	5.0X10-11	TET2
4q28.1	rs77528541	4	126843504	G/T	0.13	0.95(0.92-0.97)	1.4x10-09	-
4q34.1	rs6828523	4	175846426	C/A	0.12	0.91(0.88-0.93)	1.8X10-25	ADAM29
5p15.33	rs116095464	5	345109	T/C	0.05	1.06(1.02-1.1)	3.8x10-09	AHRR
5p15.33	rs10069690	5	1279790	C/T	0.26	1.06(1.04-1.08)	7.8X10-17	TERT
5p15.33	rs3215401	5	1296255	A/AG	0.31	0.93(0.91-0.95)	1.1X10-20	TERT
5p13.3	rs2012709	5	32567732	C/T	0.48	1.02(1-1.04)	1.2X10-08	
5p12	rs10941679	5	44706498	A/G	0.25	1.15(1.13-1.18)	5.6X10-73	
5q11.1	rs72749841	5	49641645	T/C	0.16	0.93(0.91-0.96)	7.2x10-10	-
5q11.1	rs35951924	5	50195093	A/AT	0.32	0.95(0.93-0.97)	1.3x10-11	-
5q11.2	rs62355902	5	56053723	A/T	0.16	1.18(1.15-1.21)	6.8X10-98	MAP3K1

5q11.2	rs10472076	5	58184061	T/C	0.38	1.03(1.01-1.04)	9.6X10-09	RAB3C
5q11.2	rs1353747	5	58337481	T/G	0.09	0.96(0.93-0.99)	4.1X10-09	PDE4D
5q14.2	rs7707921	5	81538046	A/T	0.25	0.96(0.94-0.98)	1.7X10-12	ATG10
5q14.39	rs10474352	5	90732225	C/T	0.16	0.94(0.92-0.97)	4.5X10-11	ARRDC3
5q22.1	rs6882649	5	111217786	T/G	0.34	0.97(0.95-0.99)	3.7x10-09	NREP
5q31.1	rs6596100	5	132407058	C/T	0.25	0.94(0.92-0.96)	7.7x10-09	HSPA4
5q33.3	rs1432679	5	158244083	T/C	0.43	1.08(1.06-1.1)	6.6X10-31	EBF1
5q35.1	rs4562056	5	169591487	G/T	0.33	1.05(1.03-1.07)	4.7x10-10	-
6p23	rs204247	6	13722523	A/G	0.44	1.04(1.02-1.06)	7.9X10-13	RANBP9
6p22.3	rs3819405	6	16399557	C/T	0.33	0.96(0.94-0.97)	1.7x10-08	ATXN1
6p22.3	rs2223621	6	20621238	C/T	0.38	1.04(1.02-1.06)	3.0x10-10	CDKAL1
6p22.2	rs71557345	6	26680698	G/A	0.07	0.92(0.88-0.96)	3.9x10-10	-
6q14.1	rs12207986	6	81094287	A/G	0.47	0.97(0.95-0.98)	1.5x10-09	-
6q14.1	rs17529111	6	82128386	T/C	0.22	1.02(1-1.04)	1.3X10-09	
6q23.1	rs6569648	6	130349119	T/C	0.24	0.94(0.92-0.96)	3.0x10-12	L3MBTL3
6q25	rs3757322	6	151942194	T/G	0.32	1.08(1.06-1.1)	3.3X10-41	ESR1
6q25	rs9397437	6	151952332	G/A	0.07	1.17(1.14-1.21)	4.8X10-54	ESR1
6q25	rs2747652	6	152437016	C/T	0.48	0.94(0.92-0.96)	1.3X10-26	ESR1
7p15.3	rs7971	7	21940960	A/G	0.35	0.96(0.94-0.98)	1.9x10-08	DNAH11, CDCA7L
7p15.1	rs17156577	7	28356889	T/C	0.11	1.05(1.02-1.08)	4.3x10-09	CREB5
7q21.2	rs6964587	7	91630620	G/T	0.39	1.03(1.02-1.05)	9.0X10-11	AKAP9
7q21.3	rs17268829	7	94113799	T/C	0.28	1.05(1.03-1.07)	4.5x10-13	-
7q22.1	rs71559437	7	101552440	G/A	0.12	0.93(0.91-0.96)	5.1x10-12	CUX1
7q32.3	rs4593472	7	130667121	C/T	0.35	0.97(0.95-0.99)	1.8X10-11	FLJ43663
7q34	rs11977670	7	139942304	G/A	0.43	1.06(1.04-1.08)	1.0X10-16	
7q35	rs720475	7	144074929	G/A	0.25	0.96(0.94-0.98)	1.2X10-11	NOBOX, ARHGEF6
8p12	rs9693444	8	29509616	C/A	0.32	1.06(1.04-1.08)	1.6X10-21	
8p11.23	rs13365225	8	36858483	A/G	0.18	0.91(0.89-0.93)	1.4X10-20	
8q21.11	rs6472903	8	76230301	T/G	0.17	0.94(0.92-0.96)	4.4X10-21	

8q21.11	rs2943559	8	76417937	A/G	0.08	1.1(1.07-1.14)	4.0X10-24	HNF4G
8q22.3	rs514192	8	102478959	T/A	0.32	1.05(1.03-1.07)	5.6x10-09	-
8q23.1	rs12546444	8	106358620	A/T	0.1	0.93(0.91-0.96)	7.5x10-11	ZFPM3
8q23.3	rs13267382	8	117209548	G/A	0.36	1.03(1.01-1.05)	1.6X10-11	LINC00536
8q24.13	rs58847541	8	124610166	G/A	0.15	1.08(1.05-1.1)	5.5x10-13	-
8q24.21	rs13281615	8	128355618	A/G	0.41	1.11(1.09-1.13)	1.9X10-57	
8q24.21	rs11780156	8	129194641	C/T	0.17	1.05(1.03-1.08)	1.1X10-13	MYC
9p21.3	rs1011970	9	22062134	G/T	0.16	1.07(1.04-1.09)	1.0X10-15	CDKN2A, CDKN2B
9q31.2	rs10759243	9	110306115	C/A	0.29	1.06(1.04-1.08)	2.2X10-18	
9q31.2	rs10816625	9	110837073	A/G	0.06	1.11(1.07-1.15)	5.0X10-18	
9q31.2	rs13294895	9	110837176	C/T	0.18	1.06(1.03-1.08)	6.5X10-17	
9q31.2	rs676256	9	110895353	T/C	0.38	0.91(0.9-0.93)	3.5X10-53	
9q33.1	rs1895062	9	119313486	A/G	0.41	0.94(0.92-0.95)	1.1x10-14	ASTN2
9q33.3	rs10760444	9	129396434	A/G	0.43	1.03(1.02-1.05)	9.1x10-09	LMX1B
9q34.2	rs8176636	9	136151579	I/D10	0.2	1.03(1.01-1.06)	1.4x10-08	ABO
10p14	rs67958007	10	9088113	TG/T	0.12	1.09(1.06-1.12)	1.7x10-10	-
10p12.31	rs7072776	10	22032942	G/A	0.29	1.05(1.03-1.07)	1.8X10-19	DNAJC1
10p12.31	rs11814448	10	22315843	A/C	0.02	1.12(1.06-1.19)	6.1X10-18	DNAJC1
10q21.2	rs10995201	10	64299890	A/G	0.16	0.9(0.88-0.92)	1.6X10-51	ZNF365
10q22.3	rs704010	10	80841148	C/T	0.38	1.07(1.05-1.09)	1.7X10-35	ZMZ1
10q23.33	rs140936696	10	95292187	C/CAA	0.18	1.04(1.02-1.07)	4.2x10-08	-
10q25.2	rs7904519	10	114773927	A/G	0.46	1.03(1.01-1.05)	1.5X10-13	TCFL2
10q26.12	rs11199914	10	123093901	C/T	0.32	0.96(0.94-0.98)	6.5X10-12	
10q26.13	rs2981578	10	123340311	T/C	0.47	1.23(1.21-1.25)	1.3X10-245	FGFR2
10q26.13	rs35054928	10	123340431	G/GC	0.4	1.27(1.25-1.3)	2.3X10-322	FGFR2
10q26.13	rs45631563	10	123349324	A/T	0.05	0.81(0.78-0.85)	7.3X10-37	FGFR2
11p15	rs6597981	11	803017	G/A	0.48	0.96(0.94-0.97)	1.4x10-12	PIDD1
11p15.5	rs3817198	11	1909006	T/C	0.32	1.05(1.03-1.07)	9.9X10-19	LSP1
11q13.1	rs3903072	11	65583066	G/T	0.47	0.97(0.95-0.99)	2.3X10-12	

11q13.3	rs554219	11	69331642	C/G	0.13	1.21(1.18-1.24)	5.8X10-47	CCND1
11q13.3	rs75915166	11	69379161	C/A	0.06	1.28(1.24-1.33)	4.1X10-95	CCND1
11q24.3	rs11820646	11	129461171	C/T	0.4	0.96(0.94-0.98)	2.1X10-14	
12p13.1	rs12422552	12	14413931	G/C	0.26	1.06(1.04-1.08)	3.6X10-15	
12p11.22	rs7297051	12	28174817	C/T	0.24	0.89(0.87-0.91)	3.0X10-60	
12q21.31	rs202049448	12	85009437	T/C	0.34	0.95(0.93-0.97)	2.7x10-08	-
12q22	rs17356907	12	96027759	A/G	0.3	0.91(0.9-0.93)	1.0X10-39	NTN4
12q24.21	rs1292011	12	115836522	A/G	0.42	0.92(0.9-0.94)	4.4X10-39	TBX3
12q24.31	rs206966	12	120832146	C/T	0.16	1.05(1.02-1.07)	3.8x10-08	-
13q13.1	rs11571833	13	32972626	A/T	0.01	1.35(1.23-1.48)	3.1X10-15	BRCA2
13q22.1	rs6562760	13	73957681	G/A	0.24	0.95(0.93-0.97)	1.5X10-09	
14q13.3	rs2236007	14	37132769	G/A	0.21	0.93(0.91-0.95)	4.2X10-21	PAX9
14q24.1	rs2588809	14	68660428	C/T	0.17	1.06(1.03-1.08)	6.3X10-14	RAD51B
14q24.1	rs999737	14	69034682	C/T	0.23	0.91(0.89-0.93)	6.5X10-39	RAD51B
14q32.11	rs941764	14	91841069	A/G	0.35	1.03(1.02-1.05)	8.2X10-13	CCDC88C
14q32.12	rs11627032	14	93104072	T/C	0.25	0.96(0.94-0.98)	4.1X10-11	RIN3
14q32.33	rs10623258	14	105212261	C/CTT	0.45	1.04(1.02-1.06)	2.3x10-08	ADSSL1
15q26.19	rs2290203	15	91512067	G/A	0.21	0.94(0.92-0.96)	8.07X10-10	PRC1
16q12.1	rs4784227	16	52599188	C/T	0.24	1.23(1.2-1.25)	6.8X10-201	TOX3
16q12.2	rs17817449	16	53813367	T/G	0.41	0.95(0.93-0.96)	2.5X10-21	FTO
16q12.2	rs11075995	16	53855291	T/A	0.24	1.03(1.01-1.06)	8.7X10-09	FTO
16q12.2	rs28539243	16	54682064	G/A	0.49	1.05(1.03-1.07)	9.1x10-15	-
16q13	rs2432539	16	56420987	G/A	0.4	1.03(1.02-1.05)	4.0x10-08	AMFR
16q23.2	rs13329835	16	80650805	A/G	0.23	1.07(1.05-1.09)	8.8X10-27	CDYL2
16q24.2	rs4496150	16	87085237	C/A	0.25	0.96(0.94-0.98)	8.1x10-09	-
17q11.2	rs146699004	17	29230520	GGT/G	0.27	0.97(0.95-0.99)	2.0X10-09	ATAD5
17q21.2	rs72826962	17	40836389	C/T	0.01	1.2(1.11-1.3)	4.6x10-09	CNTNAP1
17q21.31	rs2532263	17	44252468	G/A	0.19	0.95(0.93-0.97)	6.9x10-13	KANSL1
17q22	rs2787486	17	53209774	A/C	0.3	0.93(0.91-0.94)	5.6X10-29	

17q25.3	rs745570	17	77781725	G/A	0.5	1.03(1.01-1.05)	3.9X10-10	
18q11.2	rs527616	18	24337424	G/C	0.38	0.97(0.95-0.98)	6.7X10-15	
18q11.2	rs1436904	18	24570667	T/G	0.4	0.95(0.94-0.97)	9.9X10-15	CHST9
18q12.1	rs117618124	18	29977689	T/C	0.05	0.89(0.85-0.92)	5.5x10-12	GAREM1
18q12.3	rs6507583	18	42399590	A/G	0.07	0.92(0.89-0.96)	2.2x10-12	SETBP1
19p13.13	rs78269692	19	13158277	T/C	0.05	1.09(1.04-1.13)	1.9x10-09	NFIX1
19p13.12	rs2594714	19	13954571	G/A	0.23	0.97(0.95-0.99)	1.1x10-08	-
19p13.11	rs67397200	19	17401404	C/G	0.3	1.03(1.01-1.05)	1.6X10-08	
19p13.11	rs4808801	19	18571141	A/G	0.34	0.93(0.91-0.95)	4.7x10-28	ELL
19p13.11	rs2965183	19	19545696	G/A	0.35	1.04(1.02-1.06)	6.3x10-12	GATAD2A, MIR640
19q13.31	rs3760982	19	44286513	G/A	0.46	1.05(1.03-1.07)	1.4X10-16	KCCN4, LYPD5
19q13.22	rs71338792	19	46183031	A/AT	0.23	1.05(1.03-1.07)	3.5x10-09	GIPR
20p12.3	rs16991615	20	5948227	G/A	0.06	1.1(1.06-1.14)	1.9x10-09	MCM8
20q13.13	rs6122906	20	48945911	A/G	0.18	1.05(1.03-1.07)	2.5x10-10	-
21q21.1	rs2823093	21	16520832	G/A	0.27	0.94(0.92-0.96)	1.5X10-20	NRIP1
22q12.1	rs17879961	22	29121087	A/G	0.005	1.26(1.11-1.42)	9.7X10-09	CHEK2
22q12.2	rs132390	22	29621477	T/C	0.04	1.04(0.99-1.09)	1.2X10-08	EM1D1
22q13.1	rs738321	22	38568833	C/G	0.38	0.95(0.93-0.97)	1.0x10-13	PLA2G6
22q13.19	chr22:39359355	22	39359355	I/D10	0.1	1.1(1.07-1.14)	4.90X10-12	APOBEC3A,APOBEC3B
22q13.1	rs6001930	22	40876234	T/C	0.1	1.12(1.09-1.16)	4.4X10-34	MKL1
22q13.2	rs73161324	22	42038786	C/T	0.06	1.06(1.02-1.09)	2.0x10-09	XRCC6
22q13.31	rs28512361	22	46283297	G/A	0.11	1.05(1.02-1.08)	2.3x10-08	-

- *Build 37 position
- Chr, Chromosome; MAF, Minor Allele Frequency in controls in OncoArray dataset; OR, per-allele Odds Ratio; CI, Confidence Interval

Table S2: Dutch breast screening guideline (IKNL)[5]

	Low (<2)	**Moderate (RR: 2-3)**	**High (RR: >3)**
Life Time Risk	<20%	20-30%	>30%
Start screening	50 yr	40 yr	35 yr
Physical examination	-	-	+
Mammography	population screening*	<50 yr annual >50 yr population screening*	<60 yr annual >60 yr population screening*
MRI	-	-	-

- *Biannual mammography

Table S3: Change in risk category for family breast cancer cases and unaffected relatives

	IKNL[5]		NICE[6]		NCCN[7]	
	Lower	**Higher**	**Lower**	**Higher**	**Lower**	**Higher**
Family breast cancer cases	7.4%	12.1%	5.0%	10.8%	5.0%	4.6%
Unaffected relatives	11.1%	9.2%	8.8%	4.6%	8.4%	5.3%

- Percentages are based on the total number of family breast cancer cases and unaffected relatives, 323 and 262 respectively.
- Following the Dutch IKNL guideline, cut off levels of 20% and 30% represent low, moderate and high risk categories. Following the NICE guideline, 17% and 30% represent low, moderate and high risk categories. Following the NCCN guideline, 20% represent a cut off level for the high risk category.

Lakeman IMM, *et al. J Med Genet* 2019; 0:581–589. doi: 10.1136/jmedgenet-2019-106072

Table S4: Risk scores from individuals shown in Figure 3

	Individual	Standardised 161-SNP PRS	$BOADICEA_{LTR}$	$BOADICEA_{sPRS}$
Family A	**III-1**	0.62	0.35	0.37
	III-2	0.98	0.29	0.33
	III-3	0.86	0.40	0.44
	III-4	0.07	0.40	0.40
	IV-1	-1.54	0.24	0.20
	IV-2	-0.77	0.24	0.22
	IV-3	0.09	0.20	0.21
Family B	**II-1**	2.14	0.23	0.30
	II-2	0.20	0.32	0.33
	II-3	-0.66	0.32	0.29
	III-1	-0.62	0.20	0.18
	III-2	0.56	0.20	0.21
	III-3	-1.06	0.20	0.17
	III-4	0.81	0.20	0.22
	III-5	-0.56	0.23	0.21
	III-6	2.70	0.22	0.31
	III-7	0.16	0.21	0.22
Family C	**III-1**	1.06	0.27	0.31
	III-2	-0.50	0.31	0.29
	III-3	0.34	0.27	0.28
	III-4	0.12	0.27	0.28
	III-5	0.86	0.26	0.29
	IV-1	1.21	0.26	0.31
	IV-2	0.52	0.25	0.27
	IV-3	-1.42	0.21	0.18
	IV-4	-0.36	0.22	0.21
	IV-5	1.08	0.22	0.25
	IV-6	-0.27	0.22	0.21
	IV-7	0.95	0.22	0.25
	IV-8	0.63	0.22	0.24
	IV-9	-1.41	0.23	0.19
	IV-10	0.17	0.30	0.31
	IV-11	0.28	0.31	0.32
	IV-12	-0.57	0.29	0.27
	IV-13	-0.14	0.29	0.29
	IV-14	-0.42	0.29	0.28

- 161-SNP PRS, Polygenic Risk Score based on 161 breast cancer associated SNPs; $BOADICEA_{LTR}$, breast cancer lifetime risk at age 80, based on BOADICEA alone; $BOADICEA_{sPRS}$, 161-SNP PRS based individual breast cancer risk score.

Table S5: Mean and SD for ORIGO incident breast cancer cases subgroups

ORIGO cases subgroup	Number	Standardised 161-SNP PRS	
		Mean	SD
Non-invasive tumour*	44	0.21	0.95
Invasive tumour	313	0.37	0.91
1 invasive breast tumour	294	0.36	0.91
2 invasive breast tumours	19	0.56	1.11

- *or unknown invasiveness
- 161-SNP PRS, Polygenic Risk Score based on 161 breast cancer associated SNPs; SD, Standard Deviation

Lakeman IMM, *et al. J Med Genet* 2019; 0:581–589. doi: 10.1136/jmedgenet-2019-106072

Supplementary Figures

Figure S1

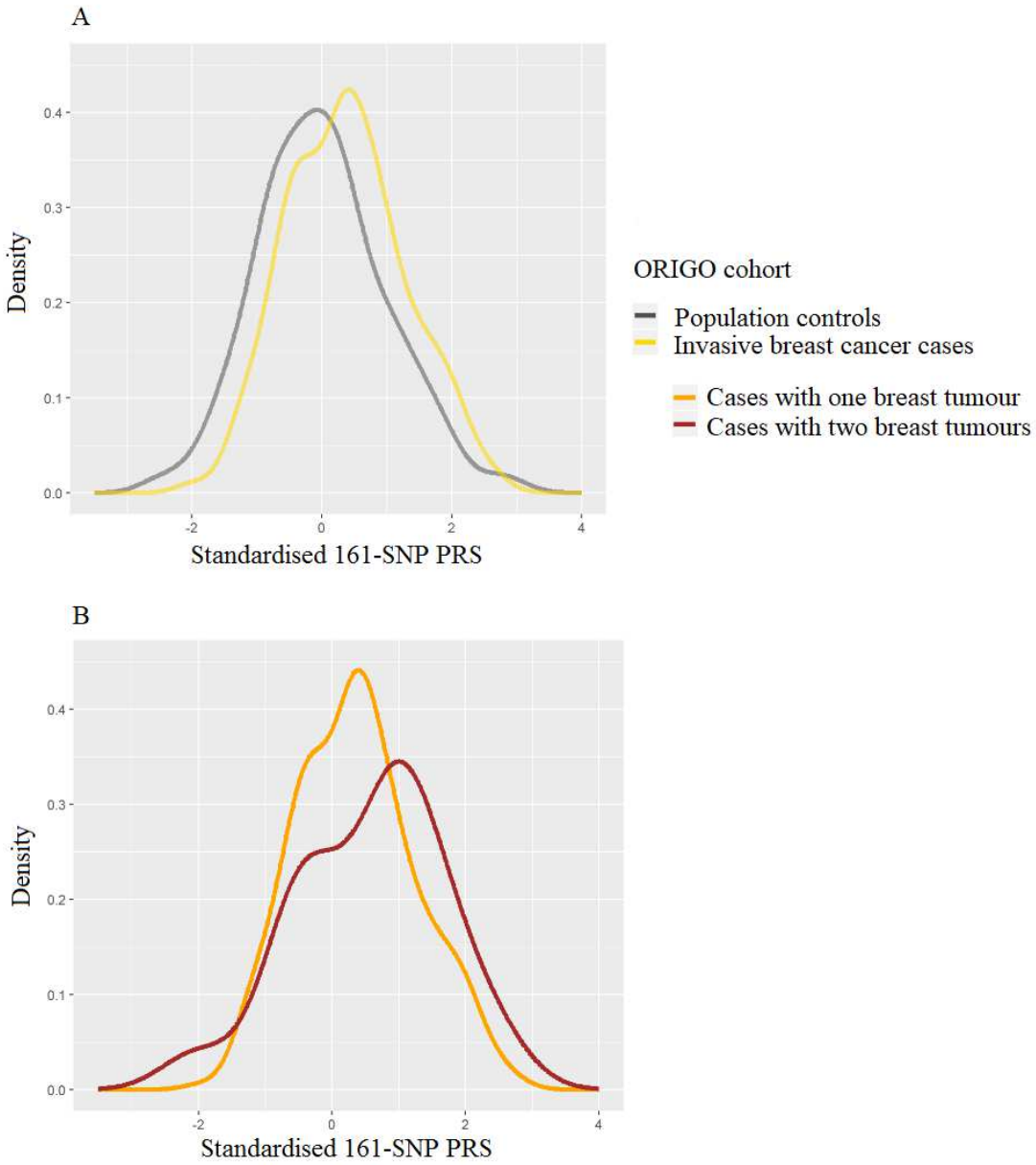

Figure S1: Distribution of the standardised 161-SNP PRS
The standardised 161-SNP PRS was plotted against the density in subgroups of the ORIGO cohort; (A) invasive breast cancer cases and population controls, (B) cases with one versus two breast tumours.

Supplementary references

1. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, Schmidt MK, Chang-Claude J, Bojesen SE, Bolla MK, Wang Q, Dicks E, Lee A, Turnbull C, Rahman N, Fletcher O, Peto J, Gibson L, Dos SS, I, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Czene K, Irwanto A, Liu J, Waisfisz Q, Meijers-Heijboer H, Adank M, van der Luijt RB, Hein R, Dahmen N, Beckman L, Meindl A, Schmutzler RK, Muller-Myhsok B, Lichtner P, Hopper JL, Southey MC, Makalic E, Schmidt DF, Uitterlinden AG, Hofman A, Hunter DJ, Chanock SJ, Vincent D, Bacot F, Tessier DC, Canisius S, Wessels LF, Haiman CA, Shah M, Luben R, Brown J, Luccarini C, Schoof N, Humphreys K, Li J, Nordestgaard BG, Nielsen SF, Flyger H, Couch FJ, Wang X, Vachon C, Stevens KN, Lambrechts D, Moisse M, Paridaens R, Christiaens MR, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer LJ, van der Schoot CE, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JI, Pita G, Alonso MR, Cox A, Brock IW, Cross SS, Reed MW, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Henderson BE, Schumacher F, Le ML, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Lindblom A, Margolin S, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Bui QM, Stone J, Dite GS, Apicella C, Tsimiklis H, Giles GG, Severi G, Baglietto L, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Muller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RA, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Durda K, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dork T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo KY, Noh DY, Matsuo K, Ito H, Iwata H, Sueta A, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Shu XO, Lu W, Gao YT, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng JH, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Shen CY, Hsiung CN, Wu PE, Ding SL, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Blot WJ, Signorello LB, Cai Q, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Simard J, Garcia-Closas M, Pharoah PD, Chenevix-Trench G, Dunning AM, Benitez J, Easton DF. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *NatGenet* 2013;45(4):353-2. doi: ng.2563 [pii];10.1038/ng.2563 [doi]
2. Michailidou K, Lindstrom S, Dennis J, Beesley J, Hui S, Kar S, Lemacon A, Soucy P, Glubb D, Rostamianfar A, Bolla MK, Wang Q, Tyrer J, Dicks E, Lee A, Wang Z, Allen J, Keeman R, Eilber U, French JD, Qing Chen X, Fachal L, McCue K, McCart Reed AE, Ghoussaini M, Carroll JS, Jiang X, Finucane H, Adams M, Adank MA, Ahsan H, Aittomaki K, Anton-Culver H, Antonenkova NN, Arndt V, Aronson KJ, Arun B, Auer PL, Bacot F, Barrdahl M, Baynes C, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Bernstein L, Blomqvist C, Bogdanova NV, Bojesen SE, Bonanni B, Borresen-Dale AL, Brand JS, Brauch H, Brennan P, Brenner H, Brinton L, Broberg P, Brock IW, Broeks A, Brooks-Wilson A, Brucker SY, Bruning T, Burwinkel B, Butterbach K, Cai Q, Cai H, Caldes T, Canzian F, Carracedo A, Carter BD, Castelao JE, Chan TL, David Cheng TY, Seng Chia K, Choi JY, Christiansen H, Clarke CL, Collee M, Conroy DM, Cordina-Duverger E, Cornelissen S, Cox DG, Cox A, Cross SS, Cunningham JM, Czene K, Daly MB, Devilee P, Doheny KF, Dork T, Dos-Santos-Silva I, Dumont M, Durcan L, Dwek M, Eccles DM, Ekici AB, Eliassen AH, Ellberg C, Elvira M, Engel C, Eriksson M, Fasching PA, Figueroa J, Flesch-Janys D, Fletcher O, Flyger H, Fritschi L, Gaborieau V, Gabrielson M, Gago-Dominguez M, Gao YT, Gapstur SM, Garcia-Saenz JA, Gaudet MM, Georgoulias V, Giles GG, Glendon G, Goldberg MS, Goldgar DE, Gonzalez-Neira A, Grenaker Alnaes GI, Grip M, Gronwald J, Grundy A, Guenel P, Haeberle L, Hahnen E, Haiman CA, Hakansson N, Hamann U, Hamel N, Hankinson S, Harrington P, Hart SN, Hartikainen JM, Hartman M, Hein A, Heyworth J, Hicks B, Hillemanns P, Ho DN, Hollestelle A, Hooning MJ, Hoover RN, Hopper JL, Hou MF, Hsiung CN,

Huang G, Humphreys K, Ishiguro J, Ito H, Iwasaki M, Iwata H, Jakubowska A, Janni W, John EM, Johnson N, Jones K, Jones M, Jukkola-Vuorinen A, Kaaks R, Kabisch M, Kaczmarek K, Kang D, Kasuga Y, Kerin MJ, Khan S, Khusnutdinova E, Kiiski JI, Kim SW, Knight JA, Kosma VM, Kristensen VN, Kruger U, Kwong A, Lambrechts D, Le Marchand L, Lee E, Lee MH, Lee JW, Neng Lee C, Lejbkowicz F, Li J, Lilyquist J, Lindblom A, Lissowska J, Lo WY, Loibl S, Long J, Lophatananon A, Lubinski J, Luccarini C, Lux MP, Ma ESK, MacInnis RJ, Maishman T, Makalic E, Malone KE, Kostovska IM, Mannermaa A, Manoukian S, Manson JE, Margolin S, Mariapun S, Martinez ME, Matsuo K, Mavroudis D, McKay J, McLean C, Meijers-Heijboer H, Meindl A, Menendez P, Menon U, Meyer J, Miao H, Miller N, Taib NAM, Muir K, Mulligan AM, Mulot C, Neuhausen SL, Nevanlinna H, Neven P, Nielsen SF, Noh DY, Nordestgaard BG, Norman A, Olopade OI, Olson JE, Olsson H, Olswold C, Orr N, Pankratz VS, Park SK, Park-Simon TW, Lloyd R, Perez JIA, Peterlongo P, Peto J, Phillips KA, Pinchev M, Plaseska-Karanfilska D, Prentice R, Presneau N, Prokofyeva D, Pugh E, Pylkas K, Rack B, Radice P, Rahman N, Rennert G, Rennert HS, Rhenius V, Romero A, Romm J, Ruddy KJ, Rudiger T, Rudolph A, Ruebner M, Rutgers EJT, Saloustros E, Sandler DP, Sangrajrang S, Sawyer EJ, Schmidt DF, Schmutzler RK, Schneeweiss A, Schoemaker MJ, Schumacher F, Schurmann P, Scott RJ, Scott C, Seal S, Seynaeve C, Shah M, Sharma P, Shen CY, Sheng G, Sherman ME, Shrubsole MJ, Shu XO, Smeets A, Sohn C, Southey MC, Spinelli JJ, Stegmaier C, Stewart-Brown S, Stone J, Stram DO, Surowy H, Swerdlow A, Tamimi R, Taylor JA, Tengstrom M, Teo SH, Beth Terry M, Tessier DC, Thanasitthichai S, Thone K, Tollenaar R, Tomlinson I, Tong L, Torres D, Truong T, Tseng CC, Tsugane S, Ulmer HU, Ursin G, Untch M, Vachon C, van Asperen CJ, Van Den Berg D, van den Ouweland AMW, van der Kolk L, van der Luijt RB, Vincent D, Vollenweider J, Waisfisz Q, Wang-Gohrke S, Weinberg CR, Wendt C, Whittemore AS, Wildiers H, Willett W, Winqvist R, Wolk A, Wu AH, Xia L, Yamaji T, Yang XR, Har Yip C, Yoo KY, Yu JC, Zheng W, Zheng Y, Zhu B, Ziogas A, Ziv E, Lakhani SR, Antoniou AC, Droit A, Andrulis IL, Amos CI, Couch FJ, Pharoah PDP, Chang-Claude J, Hall P, Hunter DJ, Milne RL, Garcia-Closas M, Schmidt MK, Chanock SJ, Dunning AM, Edwards SL, Bader GD, Chenevix-Trench G, Simard J, Kraft P, Easton DF. Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017 doi: 10.1038/nature24284 [published Online First: 2017/10/24]

3. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *American journal of human genetics* 2007;81(3):559-75. doi: 10.1086/519795 [published Online First: 2007/08/19]
4. Purcell S. PLINK version 1.7. http://pngu.mgh.harvard.edu/purcell/plink/
5. IKNL. Netherlands Comprehensive Cancer Organisation: Oncoline Mammacarcinoom. 2017. Available from: www.oncoline.nl/richtlijn/item/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=885. Accessed April, 2018
6. NICE. National Institute for Health and Care Excellence: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2013. Available from: www.nice.org.uk/guidance/cg164. Accessed April, 2018
7. NCCN. Clinical Practice Guidelines in Oncology; Breast Cancer Screening and Diagnosis. 2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed April, 2018