Supplementary Online Content

Manickam K, Buchanan AH, Schwartz MLB, et al. Exome sequencing–based screening for *BRCA1/2* expected pathogenic variants among adult biobank participants. *JAMA Netw Open.* 2018;1(5):e182140. doi:10.1001/jamanetworkopen.2018.2140

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. List of All Pathogenic and Likely Pathogenic Variants in *BRCA1* and *BRCA2* That Were Identified in Cohort

eTable 1A. *BRCA1* (NM_007294.3) Variant List

	Gene	Function	cDNA position	Protein change	pLOF	LMM variant call	ClinVar Significance	ClinVar link (accessed 1/1/18)	# cases	Cancer Reported All	Cancer Reported Women
1	*BRCA1*	Frameshift	c.68_69delAG	p.Glu23Valfs*17	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17662/	5	1 of 5 (20%)	1 of 3 (33%)
2	*BRCA1*	Frameshift	c.143delT	p.Met48Serfs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37412/	2	1 of 2 (50%)	1 of 1 (100%)
3	*BRCA1*	Missense	c.181T>G	p.Cys61Gly	No	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17661/	1	0 of 1 (0%)	0 of 1 (0%)
4	*BRCA1*	Splice variant	c.213-11T>G	NA	Yes	P	Pathogenic *2	http://www.ncbi.nlm.nih.gov/clinvar/variation/37449	1	1 of 1 (100%)	-
5	*BRCA1*	Splice variant	c.213-12A>G	NA	Yes	P	pathogenic *2	https://www.ncbi.nlm.nih.gov/clinvar/variation/37450/	1	0 of 1 (0%)	-
6	*BRCA1*	Frameshift	c.844_850dupTCATTAC	p.Gln284Leufs*5	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55735/	1	0 of 1 (0%)	-
7	*BRCA1*	Termination	c.1480C>T	p.Gln494*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37415/	3	1 of 3 (33%)	1 of 2 (50%)
8	*BRCA1*	Frameshift	c.1812delA	p.Ala605Hisfs*7	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/125513/	1	1 of 1 (100%)	1 of 1 (100%)
9	*BRCA1*	Frameshift	c.1881_1884delCAGT	p.Ser628Glufs*3	Yes	P	pathogenic *3	http://www.ncbi.nlm.nih.gov/clinvar/variation/54379	1	0 of 1 (0%)	0 of 1 (0%)
10	*BRCA1*	Frameshift	c.1953_1956delGAAA	p.Lys653Serfs*47	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37435/	2	1 of 2 (50%)	1 of 2 (50%)
11*	*BRCA1*	Frameshift	c.2090delT	p.Phe697Serfs*4	Yes	P	(novel)	https://www.ncbi.nlm.nih.gov/clinvar/variation/440454/	1	0 of 1 (0%)	0 of 1 (0%)
12	*BRCA1*	Termination	c.2309C>A	p.Ser770*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/54527/	8	4 of 8 (50%)	2 of 2 (100%)
13	*BRCA1*	Termination	c.2338C>T	p.Gln780*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/54540/	1	1 of 1 (100%)	1 of 1 (100%)
14	*BRCA1*	Frameshift	c.2443delA	p.Ile815Phefs*31	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/54572/	1	0 of 1 (0%)	-
15	*BRCA1*	Frameshift	c.2457delC	p.Asp821Ilefs*25	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37471/	1	1 of 1 (100%)	1 of 1 (100%)
16	*BRCA1*	Frameshift	c.2679_2682delGAAA	p.Lys893Asnfs*160	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37481/	1	0 of 1 (0%)	-
17	*BRCA1*	Frameshift	c.2681_2682delAA	p.Lys894Thrfs*8	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17667/	1	0 of 1 (0%)	-
18	*BRCA1*	Termination	c.2722G>T	p.Glu908*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/54657/	3	2 of 3 (67%)	2 of 3 (66%)

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19	*BRCA1*	Frameshift	c.2823delT	p.Asn941Lysfs*59	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/266306/	1	0 of 1 (0%)	0 of 1 (0%)
20	*BRCA1*	Frameshift	c.2882delA	p.Asn961Thrfs*39	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/266315/	2	1 of 2 (50%)	1 of 1 (100%)
21	*BRCA1*	Frameshift	c.3005delA	p.Asn1002Thrfs*22	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17669/	1	1 of 1 (100%)	1 of 1 (100%)
22	*BRCA1*	Termination	c.3331C>T	p.Gln1111*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/54845/	3	1 of 3 (33%)	1 of 2 (50%)
23	*BRCA1*	Frameshift	c.3481_3491delGAAGATACTAG	p.Glu1161Phefs*3	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17684/	1	0 of 1 (0%)	-
24	*BRCA1*	Frameshift	c.3485delA	p.Asp1162Valfs*48	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37531/	1	0 of 1 (0%)	-
25	*BRCA1*	Termination	c.3607C>T	p.Arg1203*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17671/	3	0 of 3 (0%)	0 of 2 (0%)
26	*BRCA1*	Frameshift	c.3648dupA	p.Ser1217Ilefs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37535/	1	0 of 1 (0%)	0 of 1 (0%)
27	*BRCA1*	Frameshift	c.3700_3704delGTAAA	p.Val1234Glnfs*8	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37542/	1	0 of 1 (0%)	-
28	*BRCA1*	Termination	c.3718C>T	p.Gln1240*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/54978/	1	0 of 1 (0%)	-
29	*BRCA1*	Frameshift	c.3767_3768delCA	p.Thr1256Argfs*10	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/182074/	2	1 of 2 (50%)	1 of 2 (50%)
30	*BRCA1*	Frameshift	c.4035delA	p.Glu1346Lysfs*20	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37560/	5	3 of 5 (60%)	3 of 5 (60%)
31	*BRCA1*	Termination	c.4222C>T	p.Gln1408*	Yes	P	pathogenic* 3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55145/	1	0 of 1 (0%)	0 of 1 (0%)
32	*BRCA1*	Termination	c.4327C>T	p.Arg1443*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17675/	1	0 of 1 (0%)	-
33	*BRCA1*	Termination	c.4389C>A	p.Tyr1463*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55187/	1	0 of 1 (0%)	0 of 1 (0%)
34	*BRCA1*	Missense	c.4484G>T	p.Arg1495Met	No	P	pathogenic *2	https://www.ncbi.nlm.nih.gov/clinvar/variation/37598/	1	0 of 1 (0%)	-
35	*BRCA1*	Splice variant	c.4485-1G>T	NA	Yes	P	pathogenic *2	https://www.ncbi.nlm.nih.gov/clinvar/variation/246501/	2	1 of 2 (50%)	0 of 1 (0%)
36	*BRCA1*	Termination	c.4524G>A	p.Trp1508*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55221/	1	0 of 1 (0%)	0 of 1 (0%)
37	*BRCA1*	Splice variant	c.4484+1G>A	NA	Yes	P	pathogenic *2	https://www.ncbi.nlm.nih.gov/clinvar/variation/37596/	1	0 of 1 (0%)	-
38	*BRCA1*	Termination	c.4689C>G	p.Tyr1563*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37607/	1	1 of 1 (100%)	1 of 1 (100%)
39	*BRCA1*	Frameshift	c.4754_4755delCA	p.Pro1585Argfs*36	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55280/	1	0 of 1 (0%)	-

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40	*BRCA1*	Missense	c.4868C>G	p.Ala1623Gly	No	LP	conflicting *1	https://www.ncbi.nlm.nih.gov/clinvar/variation/37614/	1	0 of 1 (0%)	-
41	*BRCA1*	Missense	c.5066T>G	p.Met1689Arg	No	LP	conflicting *1	https://www.ncbi.nlm.nih.gov/clinvar/variation/37625/	2	1 of 2 (50%)	1 of 2 (50%)
42	*BRCA1*	Missense	c.5096G>A	p.Arg1699Gln	No	LP	conflicting *1	https://www.ncbi.nlm.nih.gov/clinvar/variation/37636/	1	0 of 1 (0%)	0 of 1 (0%)
43	*BRCA1*	Missense	c.5123C>A	p.Ala1708Glu	No	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55407/	1	1 of 1 (100%)	1 of 1 (100%)
44	*BRCA1*	Frameshift	c.5137delG	p.Val1713*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55411/	1	0 of 1 (0%)	-
45	*BRCA1*	Splice variant	c.5153-2delA	NA	Yes	P	pathogenic *2	https://www.ncbi.nlm.nih.gov/clinvar/variation/55431/	1	0 of 1 (0%)	0 of 1 (0%)
46	*BRCA1*	Frameshift	c.5177_5180delGAAA	p.Arg1726Lysfs*3	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37644/	1	0 of 1 (0%)	-
47	*BRCA1*	Missense	c.5180G>A	p.Gly1706Glu	No	LP	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37638/	1	0 of 1 (0%)	-
48	*BRCA1*	Missense	c.5123C>A	p.Ala1708Glu	No	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55407/	1	1 of 1 (100%)	1 of 1 (100%)
49	*BRCA1*	Termination	c.5251C>T	p.Arg1751*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55480/	1	0 of 1 (0%)	-
50	*BRCA1*	Frameshift	c.5266dupC	p.Gln1756Profs*74	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/17677/	14	4 of 14 (29%)	2 of 5 (40%)
51	*BRCA1*	Termination	c.5345G>A	p.Trp1782*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55544/	2	0 of 2 (0%)	0 of 2 (0%)
52	*BRCA1*	Termination	c.5503C>T	p.Arg1835*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/55601/	1	0 of 1 (0%)	-

* Row 11- this variant was first reported by this project in ClinVar (01-2017)

eTable 1B. *BRCA2* (NM_000059.3) Variant List

	Gene	Function	cDNA position	Protein change	pLOF	LMM variant call	ClinVar Significance	ClinVar link (accessed 6/7/17)	# cases	Cancer diagnosis All	Cancer diagnosis Women
1	*BRCA2*	Frameshift	c.22_23delAG	p.Arg8Alafs*5	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51267/	1	0 of 1 (0%)	-
2	*BRCA2*	Splice variant	c.517-2A>G	NA	Yes	P	path/likely path *2	https://www.ncbi.nlm.nih.gov/clinvar/variation/51801/	1	0 of 1 (0%)	0 of 1 (0%)
3	*BRCA2*	Frameshift	c.658_659delGT	p.Val220Ilefs*4	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/9342/	2	0 of 2 (0%)	0 of 1 (0%)
4	*BRCA2*	Frameshift	c.1189_1190insTTAG	p.Gln397Leufs*25	Yes	P	pathogenic* 3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51080/	2	0 of 2 (0%)	-
5	*BRCA2*	Frameshift	c.1192delC	p.Leu398*	Yes	P	pathogenic* 2	https://www.ncbi.nlm.nih.gov/clinvar/variation/409454/	1	0 of 1 (0%)	-
6	*BRCA2*	Frameshift	c.1321_1324delACTT	p.Thr441Glnfs*18	Yes	P	pathogenic* 1	https://www.ncbi.nlm.nih.gov/clinvar/variation/418992/	1	1 of 1 (100%)	1 of 1 (100%)
7 *	*BRCA2*	Termination	c.1381G>T	p.Glu461*	Yes	P	(novel)	https://www.ncbi.nlm.nih.gov/clinvar/variation/440457/	1	0 of 1 (0%)	0 of 1 (0%)
8	*BRCA2*	Frameshift	c.1763_1766delATAA	p.Asn588Serfs*25	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51187/	1	1 of 1 (100%)	1 of 1 (100%)
9	*BRCA2*	Termination	c.1800T>G	p.Tyr600*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51199/	1	0 of 1 (0%)	0 of 1 (0%)
10	*BRCA2*	Frameshift	c.1813dupA	p.Ile605Asnfs*11	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37762/	3	1 of 3 (33%)	1 of 3 (33%)
11	*BRCA2*	Termination	c.1832C>G	p.Ser611*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/228323/	1	0 of 1 (0%)	-
12	*BRCA2*	Frameshift	c.1929delG	p.Arg645Glufs*15	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37769/	2	1 of 2 (50%)	1 of 1 (100%)
13	*BRCA2*	Frameshift	c.2092delC	p.Leu698Tyrfs*32	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37774/	1	0 of 1 (0%)	0 of 1 (0%)
14	*BRCA2*	Termination	c.2339C>G	p.Ser780*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/141070/	1	0 of 1 (0%)	-
15	*BRCA2*	Termination	c.2368G>T	p.Glu790*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/91776/	1	0 of 1 (0%)	0 of 1 (0%)
16	*BRCA2*	Termination	c.2409T>G	p.Tyr803*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37784/	1	0 of 1 (0%)	0 of 1 (0%)
17	*BRCA2*	Frameshift	c.2808_2811delACAA	p.Ala938Profs*21	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/9322/	2	1 of 2 (50%)	1 of 1 (100%)
18	*BRCA2*	Frameshift	c.3167_3170delAAAA	p.Gln1056Argfs*3	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51413/	1	0 of 1 (0%)	0 of 1 (0%)
19	*BRCA2*	Termination	c.3172A>T	p.Lys1058*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/182196/	2	0 of 2 (0%)	0 of 1 (0%)
20	*BRCA2*	Termination	c.3187C>T	p.Gln1063*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/228324/	10	0 of 10 (0%)	0 of 6 (0%)

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21	*BRCA2*	Frameshift	c.3545_3546delTT	p.Phe1182*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37846/	6	0 of 6 (0%)	0 of 2 (0%)
22	*BRCA2*	Frameshift	c.3680_3681delTG	p.Leu1227Glnfs*5	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51504/	1	0 of 1 (0%)	-
23	*BRCA2*	Frameshift	c.3847_3848delGT	p.Val1283Lysfs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37859/	5	2 of 5 (40%)	1 of 3 (33%)
24 *	*BRCA2*	Frameshift	c.4103delT	p.Leu1368Tyrfs*6	Yes	P	(novel)	https://www.ncbi.nlm.nih.gov/clinvar/variation/440456/	1	0 of 1 (0%)	0 of 1 (0%)
25	*BRCA2*	Frameshift	c.4284dupT	p.Gln1429Serfs*9	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37892/	2	0 of 2 (0%)	0 of 2 (0%)
26	*BRCA2*	Frameshift	c.4419delC	p.Asn1473Lysfs*6	Yes	P	Pathogenic *1	https://www.ncbi.nlm.nih.gov/clinvar/variation/420191/	1	0 of 1 (0%)	0 of 1 (0%)
27	*BRCA2*	Termination	c.4588A>T	p.Lys1530*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51678/	1	0 of 1 (0%)	0 of 1 (0%)
28	*BRCA2*	Frameshift	c.4876_4877delAA	p.Asn1626Serfs*12	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37929/	2	0 of 2 (0%)	0 of 1 (0%)
29	*BRCA2*	Termination	c.4889C>G	p.Ser1630*	Yes	P	Pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51732/	1	0 of 1 (0%)	0 of 1 (0%)
30	*BRCA2*	Frameshift	c.4936_4939delGAAA	p.Glu1646Glnfs*23	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37935/	1	0 of 1 (0%)	0 of 1 (0%)
31	*BRCA2*	Termination	c.4965C>G	p.Tyr1655*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37936/	14	1 of 14 (7%)	1 of 8 (12%)
32	*BRCA2*	Frameshift	c.4947_4948delAA	p.Pro1651Cysfs*14	Yes	P	Pathogenic* 3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51747/	1	0 of 1 (0%)	0 of 1 (0%)
33	*BRCA2*	Frameshift	c.5073dupA	p.Trp1692Metfs*3	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37943/	2	0 of 2 (0%)	-
34	*BRCA2*	Frameshift	c.5157_5161delTTCAA	p.Asn1719Lysfs*6	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51780/	3	1 of 3 (33%)	-
35	*BRCA2*	Frameshift	c.5217_5220delTTTA	p.Tyr1739*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51820/	1	0 of 1 (0%)	-
36	*BRCA2*	Frameshift	c.5350_5351delAA	p.Asn1784Hisfs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37959/	2	1 of 2 (50%)	1 of 1 (100%)
37 *	*BRCA2*	Frameshift	c.5352dupC	p.Thr1785Hisfs*2	Yes	P	(novel)	https://www.ncbi.nlm.nih.gov/clinvar/variation/548420/	2	1 of 2 (50%)	1 of 1 (100%)
38	*BRCA2*	Frameshift	c.5410_5411delGT	p.Val1804Lysfs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37963/	1	0 of 1 (0%)	-
39	*BRCA2*	Frameshift	c.5576_5579delTTAA	p.Ile1859Lysfs*3	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37975/	1	0 of 1 (0%)	-
40	*BRCA2*	Termination	c.5614A>T	p.Lys1872*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37979/	1	0 of 1 (0%)	0 of 1 (0%)
41	*BRCA2*	Frameshift	c.5681dupA	p.Tyr1894*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/37988/	1	0 of 1 (0%)	0 of 1 (0%)

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42	*BRCA2*	Frameshift	c.5722_5723delCT	p.Leu1908Argfs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/9320/	24	7 of 24 (29%)	5 of 15 (33%)
43	*BRCA2*	Termination	c.5857G>T	p.Glu1953*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/51952/	1	0 of 1 (0%)	0 of 1 (0%)
44	*BRCA2*	Frameshift	c.5946delT	p.Ser1982Argfs*22	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/9325/	3	0 of 3 (0%)	0 of 1 (0%)
45	*BRCA2*	Termination	c.6037A>T	p.Lys2013*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38016/	5	0 of 5 (0%)	0 of 1 (0%)
46	*BRCA2*	Frameshift	c.6405_6409delCTTAA	p.Asn2135Lysfs*3	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38043/	1	0 of 1 (0%)	0 of 1 (0%)
47	*BRCA2*	Frameshift	c.6468_6469delTC	p.Gln2157Ilefs*18	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38047/	1	0 of 1 (0%)	-
48	*BRCA2*	Frameshift	c.6644_6647delACTC	p.Tyr2215Serfs*13	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38060/	3	0 of 3 (0%)	0 of 3 (0%)
49	*BRCA2*	Frameshift	c.6998dupT	p.Pro2334Thrfs*6	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/219496/	1	0 of 1 (0%)	-
50	*BRCA2*	Frameshift	c.7069_7070delCT	p.Leu2357Valfs*2	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38082/	18	2 of 18 (11%)	1 of 12 (8%)
51	*BRCA2*	Splice variant	c.7436-2A>T	NA	Yes	P	pathogenic *1	http://www.ncbi.nlm.nih.gov/clinvar/variation/52330	1	0 of 1 (0%)	-
52	*BRCA2*	Termination	c.7558C>T	p.Arg2520*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/52353/	2	1 of 2 (50%)	1 of 2 (50%)
53	*BRCA2*	Frameshift	c.7762delA	p.Ile2588Tyrfs*60	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/52405/	2	1 of 2 (50%)	0 of 1 (0%)
54	*BRCA2*	Missense	c.7878G>C	p.Trp2626Cys	No	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38125/	2	0 of 2 (0%)	0 of 1 (0%)
55	*BRCA2*	Missense	c.8243G>A	p.Gly2748Asp	No	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/52535/	1	0 of 1 (0%)	0 of 1 (0%)
56	*BRCA2*	Splice variant	c.8487+1G>A	NA	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/52602/	3	1 of 3 (33%)	0 of 1 (0%)
57	*BRCA2*	Termination	c.8489G>A	p.Trp2830*	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/52605/	2	0 of 2 (0%)	-
58	*BRCA2*	Frameshift	c.8537_8538delAG	p.Glu2846Glyfs*22	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/9328/	1	0 of 1 (0%)	-
59	*BRCA2*	Splice variant	c.8755-1G>A	NA	Yes	P	Uncertain significance *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38183/	1	0 of 1 (0%)	-
60	*BRCA2*	Frameshift	c.8904delC	p.Thr2968Cysfs*7	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38192/	4	2 of 4 (50%)	2 of 3 (66%)
61	*BRCA2*	Splice variant	c.8953+1G>T	NA	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38198/	3	0 of 3 (0%)	0 of 1 (0%)
62	*BRCA2*	Missense	c.9004G>A	p.Glu3002Lys	No	P	conflicting *1	https://www.ncbi.nlm.nih.gov/clinvar/variation/38201/	1	0 of 1 (0%)	-

	Gene	Function	cDNA position	Protein change	pLOF	LMM variant call	ClinVar Significance	ClinVar link (accessed 1/1/18)	# cases	Cancer Reported All	Cancer Reported Women
63	*BRCA2*	Frameshift	c.9097dupA	p.Thr3033Asnfs*11	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/38208/	1	0 of 1 (0%)	0 of 1 (0%)
64	*BRCA2*	Frameshift	c.9253delA	P.Thr3085Glnfs*19	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/52785/	3	1 of 3 (33%)	1 of 2 (50%)
65	*BRCA2*	Frameshift	c.9672dupA	p.Tyr3225Ilefs*30	Yes	P	pathogenic *3	https://www.ncbi.nlm.nih.gov/clinvar/variation/126217/	1	0 of 1 (0%)	-
66 *	*BRCA2*	Frameshift	c.9777delT	p.Ile3259Metfs*16	Yes	LP	(novel)	NA	1	0 of 1 (0%)	0 of 1 (0%)

* Row 7- this variant was first reported by this project in ClinVar (01-2017)

* Row 24 - this variant was first reported by this project in ClinVar (12-2016)

* Row 37 – this variant was first reported by this project in ClinVar (08-2017)

* Row 66 - report of this variant in ClinVar by this project is pending

eTable 2. The Overall Prevalence and Prevalence Controlling for Relatedness

The overall prevalence in the entire cohort (N=50,726) and the prevalence in a subcohort (N=38,339) where only one individual in every first and second degree relationship was included. The algorithm for determining relatedness has been described (Ref 19, 25)

COHORT N	**CASES** N (%)	**PREVALENCE**
50726	267 (0.53)	1/190
38339	213 (0.56)	1/180

eTable 3. Cause of Death Analysis

Among the 23 cases of individuals with P/LP *BRCA1/2* variants there were 11 (47.8%) cases with relevant cancers, and at least 9 (39.1%) died of HBOC associated disease.

		Cause of Death			Family History (EHR based)		HBOC Associated cancers				
	N=23	BRCA associated (N=9)	Non-BRCA Associated (N=11)	Unknown (N=3)	Family History (+) (N=10)	Family History (-) (N=13)	Breast	Ovarian	Prostate	Pancreatic	None
Female	12	7	3	2	8	4	4	5	-	0	3
Male	11	2	8	1	2	9	0	-	1	1	9
BRCA1	9	4	4	1	5	4	1	3	0	0	5
BRCA2	14	5	7	2	5	9	3	2	1	1	7
Prior Testing	4	4	0	0	4	0	2	2	0	0	0
No Prior Testing	19	5	11	3	6	13	2	3	1	1	12

eTable 4. Relevant Cancer Among the Living Cases

18.4% (45/244) of living *BRCA1/2* cases were found to have relevant cancer diagnoses. The cancers are broken down by anatomic sites in women v. men, BRCA1 v. BRCA2, and in those with and without prior testing.

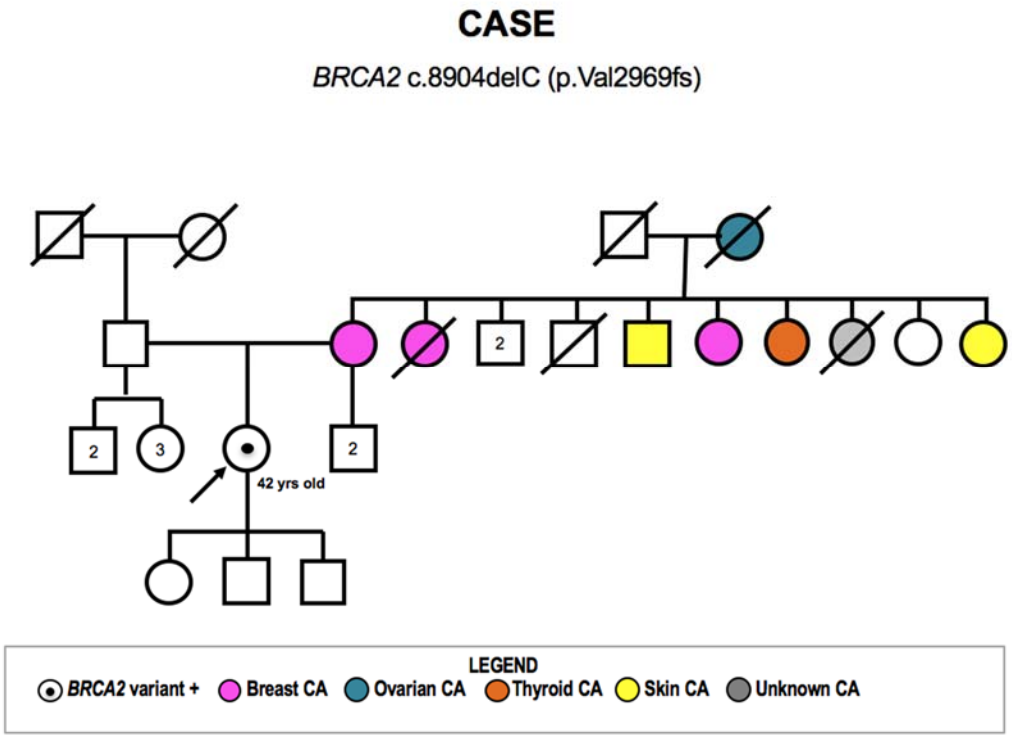
		Family History (EHR based)		**HBOC Associated cancers**				
	N=244	Family History (+) (N=129)	Family History (-) (N=115)	Breast (N=27)	Ovarian N=10	Prostate (N=9)	Melanoma (N=2)	None (N=199)
Female *	136	91	45	27 *	10 *	-	0	102
Male	108	38	70	0	-	9	2	97
BRCA1	87	51	36	14	7	4	2	61
BRCA2	157	78	79	13	3	5	0	138
Prior Testing	44	38	6	11	4	1	0	30
No Prior Testing	200	91	109	16	6	8	2	169

* three cases of women wih breast and ovarian cancer

eTable 5. Table Demonstrating Groupings for Odds Ratio Calculations for Figure 2B-D

	Cases Pos P/LP	Controls Neg P/LP
Cancer	a	b
No cancer	c	d
$\frac{a/c}{b/d}$		

eFigure 1. Pedigree and Case Story



42-year-old woman with new diagnosis of bilateral ductal carcinoma in situ (DCIS). A woman with no previous cancer diagnosis received notification of a pathogenic *BRCA2* variant (c.8904delC - ClinVar 38192). Her family history is significant for the following HBOC related cancers: mother diagnosed with breast cancer at age 54 (living), maternal aunt diagnosed with breast cancer at age 39 (deceased), a second maternal aunt diagnosed with breast cancer at age 38 (living), and maternal grandmother diagnosed with ovarian cancer at age 38 (deceased). She had a mammogram that was previously recommended but never carried out. A left breast abnormality on this screening mammogram prompted a biopsy, leading to a diagnosis of DCIS. Subsequent bilateral breast MRI showed no further abnormalities in either breast. She proceeded to bilateral mastectomies, with pathology showing residual DCIS in the left breast and an occult DCIS in the right breast. She was thereby the fourth case of a "group 3" diagnosis (see Table 2) in addition to the three cases described in Buchanan et al.[21]

eFigure 2. Family Health History in EHR of *BRCA1/2* Cases (Women and Men)

Panel A (top). Data extraction from the pre-return of results EHR of all BRCA1/2 carriers.

Panel B (bottom). Data extraction from the post-return of results EHR of a subset of BRCA1/2 carriers who reviewed Family Health History with a genetic counselor.

Note: In both settings there were twice as many men with no recorded family history of relevant disease in their EHR compared to women.