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Progress in clinical interpretation of DNA variants of uncertain significance in BRCA1 and BRCA2. By N.M. Lindor, S. Friedman, L. Guidugli, S. Tavtigian, D. Goldgar, F. Couch.

Based on a publication titled "A review of a multifactorial probability-based model for classification of *BRCA1* and *BRCA2* variants of uncertain significance (VUS)" in Human Mutation, January 2012

Introduction: Testing of the BRCA1 and BRCA2 genes identifies individuals at elevated risk of breast and ovarian cancer due to mutations in these genes. However, not everyone who has their DNA tested for BRCA1/2 mutations gets a clear yes or no answer. Some tests discover DNA variants of uncertain significance (VUS). People found to have a VUS cannot be counseled that they have cancer risks like those with definite BRCA mutations, nor can they be counseled that they are not BRCA gene mutation carriers. Also, a VUS cannot be used to test for cancer risks among relatives of the tested individual.

Recently, a new model was developed for attempting to interpret the meaning of some of the VUS in the BRCA genes. The process combines multiple lines of evidence to produce a number, called the posterior probability. This score reflects the chance that a VUS is or is not likely to be a real BRCA mutation or is a harmless finding.

Three tables at the end of this article list specific BRCA VUS results that based on new analysis are now scored as either similar in significance to typical BRCA mutations or those that seem unlikely to be involved with causing cancer. If you're a patient who has ever received a report of a VUS in a BRCA gene, you may want to look at the tables to see if your VUS is listed. If your VUS is listed, consider contacting your genetic health care provider to discuss this possible change in clinical interpretation.

How can the new VUS scores be used for medical decision making? When the scores reach a certain level, it has been proposed that it may be reasonable to use the reclassified results to guide medical decisions. [Plon, et al., 2008] Scores were grouped into five levels, shown in Table 1. A VUS that ends up being class 4 or 5 can be managed in the same way as typical mutations in BRCA genes. That is, the evidence available about this VUS is convincing enough to think that this particular VUS may in fact have the medical significance of a typical BRCA mutation. Therefore, people carrying such VUS may be best served by proceeding with medical decision making based on this prediction. In addition, relatives could be checked for the same mutation and also managed based on their test results.

On the other hand, a VUS classified as class 1 or 2 means that the DNA alteration is **not** likely to increase cancer risk by disturbing the normal function of the BRCA1/2 genes. Testing for the VUS should **not** be offered to relatives as a means to determine their risk. It likely is not the answer for that person or family.

Many VUS will remain in the category 3 until more evidence becomes available. Category 3

VUS are still truly of uncertain significance and are thought to be best managed based on the family history and other risk factors. DNA testing results should not be used in medical decision making or predictive testing for relatives.

Tables 2 to 4 list many specific VUS in both BRCA1 and BRCA2 that are now reclassified. The likelihood that this variant is pathogenic, which means increased risk of cancer, is shown by the posterior probability score. This number is mapped for you to one of the five clinical categories in Table 1.

Table 1. Proposed classification for DNA sequence variants and correlation of clinical recommendation with probability that any given alteration is deleterious (i.e., increases chance for disease related to malfunction of a gene). [Adapted from Plon, et al., 2008]

Class	Definition	Posterior probability	Clinical testing	Surveillance recommendations
5	Definitely pathogenic	>0.99	Test at-risk relatives for the variant	Full high-risk surveillance
4	Likely pathogenic	0.95-0.99	Test at-risk relatives for the variant	Full high-risk surveillance
3	Uncertain	0.05-0.949	Do not use as predictive testing in at-risk relatives	Counsel based on family history and other risk factors
2	Likely not pathogenic	0.001-0.049	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected
1	Not Pathogenic	<0.001	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected

Caution: It is extremely important to use this posterior probability model cautiously. In arriving at the numbers for each VUS, a number of educated assumptions had to be made and because of this, there is the possibility that a VUS can still be misclassified by this approach. The scientists working on BRCA VUS have made a good-faith effort to attempt interpretation for the benefit of the many individuals who have received these VUS results, but there is no foolproof way to prove what is right and what might be mistaken. To be cautious, the group that developed these new classifications [Plon, et al, 2008] insisted that more than one line of information was required before a VUS could be placed into the class 1, 2, 4, or 5 categories.

What now? If you found your VUS on these tables and if it seems that this sheds a different light on your situation, take this article to your genetic medical provider and discuss your own situation to see if any change in your medical care might be warranted.

Table 2: BRCA1 VUS classified as class 1, 2 or class 4, 5. Note that the numbering system for BRCA1 variants has evolved over time so the original terminology (BIC) and the newer

terminology (HGVS) are shown side by side, as some individuals may have reports on file that use one or the other of these. The IARC class refers back to Table 1 in this article.

Technical note: GenBank Reference BRCA1 U14680.1 Nucleotide numbering in "HGVS: DNA level" reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1. Nucleotide numbering in "BIC: DNA level" refers to the original nomenclature for BRCA1 and BRCA2 before adoption of HGVS standards where BRCA1 +119 and BRCA2 +228 correspond to the A of the ATG translation initiation codons in the reference sequence.

BRCA1 exon	Codon	HGVS: protein level	BIC: DNA level	HGVS: DNA level	Posterior probability of being deleterious	IARC class
2	M18T	p.Met18Thr	172T>C	c.53T>C	0.98	4
2	L22S	p.Leu22Ser	184T>C	c.65T>C	0.99	5
3	T37K	p.Thr37K	229C>A	c.110C>A	1.00	5
3	C39R	p.Cys39Arg	234T>C	c.115T>C	0.99	5
3	C44S	p.Cys44Ser	249T>A	c.130T>A	1.00	5
3	C44Y	p.Cys44Tyr	250G>A	c.131G>A	1.00	5
3	K45Q	p.Lys45Gln	252A>C	c.133A>C	8.00×10^{-4}	1
5	C61G	p.Cys61Gly	300T>G	c.181T>G	1.00	5
5	D67Y	p.Asp67Tyr	318G>T	c.199G>T	2.90×10^{-6}	1
7	Y105C	p.Tyr105Cys	433A>G	c.314A>G	1.05×10^{-7}	1
7	I124V	p.Ile124Val	489A>G	c.370A>G	1.39×10^{-4}	1
7	N132K	p.Asn132Lys	515C>A	c.396C>A	1.66×10^{-4}	1
7	P142H	p.Pro142His	544C>A	c.425C>A	1.03×10^{-6}	1
7	E143K	p.Glu143Lys	546G>A	c.427G>A	1.09×10^{-5}	1
8	Q155E	p.Gln155Glu	582C>G	c.463C>G	3.89×10^{-5}	1
8	Y179C	p.Tyr179Cys	655A>G	c.536A>G	1.73×10^{-12}	1
9	S186Y	p.Ser186Tyr	676C>A	c.557C>A	7.82×10^{-12}	1
9	V191I	p.Val191Ile	690G>A	c.571G>A	1.57×10^{-7}	1
11	L246V	p.Leu246Val	855T>G	c.736T>G	5.31×10^{-7}	1
11	A280G	p.Ala280Gly	958C>G	c.839C>G	7.67×10^{-5}	1
11	M297I	p.Met297Ile	1010G>A	c.891G>A	6.34×10^{-5}	1
11	P334H	p.Pro334His	1120C>A	c.1001C>A	0.02	2
11	P334L	p.Pro334Leu	1120C>T	c.1001C>T	2.71×10^{-7}	1
11	Q356R	p.Gln34Arg	1186A>G	c.1067A>G	$<2.04\times10^{-12}$	1
11	D369del	p.Asp369del	1225del3	c.1105_1107del	6.13×10^{-6}	1
11	D369N	p.Asp369Asn	1224G>A	c.1105G>A	5.68×10^{-6}	1
11	D420Y	p.Asp420Tyr	1377G>T	c.1258G>T	1.66×10^{-4}	1
11	N473S	p.Asn473Ser	1537A>G	c.1418A>G	3.37×10^{-6}	1
11	F486L	p.Phe486Leu	1575T>C	c.1456T>C	1.86×10^{-12}	1
11	R496H	p.Arg496His	1606G>A	c.1487G>A	1.88×10^{-6}	1
11	R496C	p.Arg496Cys	1605C>T	c.1486C>T	8.91×10^{-4}	1

11	R504H	p.Arg504His	1630G>A	c.1511G>A	$1.06x10^{-6}$	1
11	N550H	p.Asn550His	1767A>C	c.1648A>C	$1.63x10^{-12}$	1
11	E597K	p.Glu597Lys	1908G>A	c.1789G>A	$6.92x10^{-11}$	1
11	A622V	p.Ala622Val	1984C>T	c.1865C>T	$2.12x10^{-5}$	1
11	D642H	p.Asp642His	2043G>C	c.1924G>C	$1.40x10^{-5}$	1
11	K654Q	p.Lys654Gln	2079A>C	c.1960A>C	$6.86x10^{-3}$	2
11	L668F	p.Leu668Phe	2121C>T	c.2002C>T	$1.94x10^{-4}$	1
11	D693N	p.Asp693Asn	2196G>A	c.2077G>A	$2.04x10^{-12}$	1
11	N723D	p.Asn723Asp	2286A>G	c.2167A>G	$3.17x10^{-10}$	1
11	E736A	p.Glu736Ala	2326A>C	c.2207A>C	$9.62x10^{-3}$	2
11	V772A	p.Val772Ala	2434T>C	c.2315T>C	$1.92x10^{-7}$	1
11	Q804H	p.Gln804His	2531G>C	c.2412G>C	$4.46x10^{-4}$	1
11	N810Y	p.Asn810Tyr	2547A>T	c.2428A>T	$2.33x10^{-13}$	1
11	K820E	p.Lys820Gln	2577A>G	c.2458A>G	$<2.04x10^{-12}$	1
11	T826K	p.Thr826Lys	2596C>A	c.2477C>A	$2.03x10^{-9}$	1
11	R841W	p.Arg841Trp	2640C>T	c.2521C>T	$2.29x10^{-12}$	1
11	E842G	p.Glu842Gly	2644A>G	c.2525A>G	$4.30x10^{-6}$	1
11	Y856H	p.Tyr856His	2685T>C	c.2566T>C	$1.80x10^{-4}$	1
11	K862E	p.Lys862Glu	2703A>G	c.2584A>G	$9.91x10^{-6}$	1
11	R866C	p.Arg866Cys	2715C>T	c.2596C>T	$1.63x10^{-14}$	1
11	P871L	p.Pro871Leu	2731C>T	c.2612C>T	$<2.04x10^{-12}$	1
11	G890V	p.Gly890Val	2788G>T	c.2669G>T	$4.08x10^{-6}$	1
11	V920A	p.Val920Ala	2878T>C	c.2759T>C	0.02	2
11	I925L	p.Ile925Leu	2892A>C	c.2773A>C	$3.26x10^{-6}$	1
11	M1008I	p.Met1008Ile	3143G>A	c.3024G>A	$1.96x10^{-8}$	1
11	M1008V	p.Met1008Val	3141A>G	c.3022A>G	$<2.04x10^{-12}$	1
11	R1028H	p.Arg1028His	3202G>A	c.3083G>A	$9.98x10^{-6}$	1
11	E1038G	p.Gln1038Gly	3232A>G	c.3113A>G	$<2.04x10^{-12}$	1
11	S1040N	p.Ser1040Asn	3238G>A	c.3119G>A	$<2.04x10^{-12}$	1
11	I1044V	p.Ile1044Val	3249A>G	c.3130A>G	$2.34x10^{-6}$	1
11	P1099L	p.Pro1099Leu	3415C>T	c.3296C>T	$3.09x10^{-11}$	1
11	S1101N	p.Ser1101Asn	3421G>A	c.3302G>A	$6.32x10^{-9}$	1
11	K1109N	p.Lys1109Asn	3446A>C	c.3327A>C	$3.07x10^{-5}$	1
11	S1140G	p.Ser1140Gly	3537A>G	c.3418A>G	$5.92x10^{-6}$	1
11	D1155H	p.Asp1155His	3582G>C	c.3463G>C	$7.14x10^{-6}$	1
11	K1183R	p.Lys1183Arg	3667A>G	c.3548A>G	$<2.04x10^{-12}$	1
11	Q1200H	p.Gln1200His	3719G>C	c.3600G>C	$7.09x10^{-3}$	2
11	R1203Q	p.Arg1203Gln	3727G>A	c.3608G>A	$3.65x10^{-6}$	1
11	E1214K	p.Glu1214Lys	3759G>A	c.3640G>A	$6.89x10^{-10}$	1
11	P1238L	p.Pro1238Leu	3832C>T	c.3713C>T	$1.94x10^{-8}$	1
11	V1247I	p.Val1247Ile	3858G>A	c.3739G>A	$2.51x10^{-6}$	1
11	E1250K	p.Glu1250Lys	3867G>A	c.3748G>A	$2.04x10^{-7}$	1
11	S1266T	p.Ser1266Thr	3916G>C	c.3797G>C	$1.13x10^{-6}$	1
11	I1275V	p.Ile1275Val	3942A>G	c.3823A>G	$3.31x10^{-7}$	1
11	R1347G	p.Arg1347Gly	4158A>G	c.4039A>G	$<2.04x10^{-12}$	1
11	T1349M	p.Thr1349Met	4165C>T	c.4046C>T	$4.42x10^{-5}$	1

11	M1361L	p.Met1361Leu	4200A>C	c.4081A>C	$1.96x10^{-4}$	1
13	H1402Y	p.His1402Tyr	4323C>T	c.4204C>T	$1.87x10^{-4}$	1
13	E1419Q	p.Glu1419Gln	4374G>C	c.4255G>C	$1.52x10^{-4}$	1
13	R1443G	p.Arg1443Gly	4446C>G	c.4327C>G	$<6.18x10^{-4}$	1
14	N1468H	p.Asn1468His	4521A>C	c.4402A>C	$9.18x10^{-5}$	1
14	[a]R1495M	p.Arg1495Met	4603G>T	c.4484G>T	1.00	5
15	S1512I	p.Ser1512Ile	4654G>T	c.4535G>T	$<3.09x10^{-12}$	1
15	V1534M	p.Val1534Met	4719G>A	c.4600G>A	$7.40x10^{-11}$	1
15	D1546N	p.Asp1546Asn	4755G>A	c.4636G>A	$1.73x10^{-4}$	1
15	D1546Y	p.Asp1546Tyr	4755G>T	c.4636G>T	$2.84x10^{-5}$	1
16	L1564P	p.Leu1564Pro	4810T>C	c.4691T>C	$1.02x10^{-4}$	1
16	S1613G	p.Ser1613Gly	4956A>G	c.4837A>G	$<3.09x10^{-12}$	1
16	P1614S	p.Pro1614Ser	4959C>T	c.4840C>T	$7.03x10^{-11}$	1
16	M1628T	p.Met1628Thr	5002T>C	c.4883T>C	$4.95x10^{-6}$	1
16	P1637L	p.Pro1637Leu	5029C>T	c.4910C>T	$6.27x10^{-5}$	1
16	M1652I	p.Met1652Ile	5075G>A	c.4956G>A	$1.48x10^{-5}$	1
16	M1652T	p.Met1652Thr	5074T>C	c.4955T>C	$1.10x10^{-4}$	1
16	F1662S	p.Phe1662Ser	5104T>C	c.4985T>C	$1.61x10^{-4}$	1
17	E1682K	p.Glu1682Lys	5163G>A	c.5044G>A	$9.76x10^{-5}$	1
17	T1685A	p.Thr1685Ala	5172A>G	c.5053A>G	1.00	5
17	T1685I	p.Thr1685Ile	5173C>T	c.5054C>T	1.00	5
17	V1688del	p.Val1688del	5181del3	c.5181_5183del GTT	1.00	5
17	M1689R	p.Met1689Arg	5185T>G	c.5066T>G	0.989	4
18	R1699Q	p.Arg1699Gln	5215G>A	c.5096G>A	1.00	5
18	R1699W	p.Arg1699Trp	5214C>T	c.5095C>T	1.00	5
18	G1706A	p.Gly1706Ala	5236G>C	c.5117G>C	$4.95x10^{-5}$	1
18	G1706E	p.Gly1706Glu	5236G>A	c.5117G>A	1.00	5
18	A1708E	p.Ala1708Glu	5242C>A	c.5123C>A	1.00	5
18	S1715R	p.Ser1715Arg	5262A>C	c.5143A>C	0.99	5
19	T1720A	p.Thr1720Ala	5277A>G	c.5158A>G	$3.44x10^{-13}$	1
20	G1738R	p.Gly1738Arg	5331G>A	c.5212G>A	1.00	5
20	R1751Q	p.Arg1751Gln	5371G>A	c.5252G>A	$2.06x10^{-4}$	1
21	L1764P	p.Leu1764Pro	5410T>C	c.5291T>C	0.99	5
21	I1766S	p.Ile1766Ser	5416T>G	c.5297T>G	1.00	5
21	M1775K	p.Met1775 Lys	5443T>A	c.5324T>A	1.00	5
21	M1775R	p.Met1775Arg	5443T>G	c.5324T>G	1.00	5
21	P1776H	p.Pro1776His	5446C>A	c.5327C>A	0.03	2
22	C1787S	p.Cys1787Ser	5478T>A	c.5359T>A	1.00	5
22	G1788V	p.Gly1788Val	5482G>T	c.5363G>T	1.00	5
23	V1804D	p.Val1804Asp	5530T>A	c.5411T>A	$3.74x10^{-5}$	1
24	V1838E	p.Val1838Glu	5632T>A	c.5513T>A	1.00	5
24	I1858L	p.Ile1858Leu	5691A>C	c.5572A>C	$6.97x10^{-5}$	1
24	P1859R	p.Pro1859Arg	5695C>G	c.5576C>G	$1.04x10^{-6}$	1

Table 3: BRCA2 VUS classified as class 1, 2 or class 4, 5. Note that the numbering system for BRCA2 variants has evolved over time so the original terminology (BIC) and the newer terminology (HGVS) are shown side by side, as some individuals may have reports on file that use one or the other of these. The IARC class refers back to Table 1 in this article. Technical note: GenBank Reference BRCA2 NM_000059.3 Nucleotide numbering in "HGVS: DNA level" reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.

BRCA2 exon	Codon	HGVS: protein level	BIC: DNA level	HGVS: DNA level	Posterior probability of being deleterious	IARC class
2	R18H	p.Arg18His	281G>A	c.53G>A	3.50×10^{-4}	1
3	Y42C	p.Tyr42Cys	353A>G	c.125A>G	1.22×10^{-18}	1
3	N56T	p.Asn56Thr	395A>C	c.167A>C	3.06×10^{-6}	1
3	A75P	p.Ala75Pro	451G>C	c.223G>C	9.28×10^{-9}	1
6	P168T	p.Pro168Thr	730C>A	c.502C>A	3.16×10^{-5}	1
10	N319T	p.Asn319Thr	1184A>C	c.956A>C	4.01×10^{-4}	1
10	S326R	p.Ser326Arg	1206C>A	c.978C>A	5.83×10^{-4}	1
10	N372H	p.Asn372His	1342C>A	c.1114C>A	2.04×10^{-9}	1
10	P375S	p.Pro375Ser	1351C>T	c.1123C>T	6.48×10^{-5}	1
10	S384F	p.Ser384Phe	1379C>T	c.1151C>T	4.24×10^{-4}	1
10	E462G	p.Glu462Gly	1613A>G	c.1385A>G	2.93×10^{-6}	1
10	A487E	p.Ala487Glu	1688C>A	c.1440C>A	3.52×10^{-3}	2
10	K513R	p.Lys513Arg	1766A>G	c.1538A>G	1.89×10^{-4}	1
10	N517S	p.Asn517Ser	1778A>G	c.1550A>G	2.54×10^{-2}	2
10	C554W	p.Cys554Trp	1890T>G	c.1662T>G	3.96×10^{-7}	1
10	T582P	p.Thr582Pro	1972A>C	c.1744A>C	2.24×10^{-5}	1
10	N588D	p.Asn588Asp	1990A>G	c.1762A>G	3.00×10^{-2}	2
10	G602R	p.Gly602Arg	2032G>A	c.1804G>A	1.01×10^{-7}	1
10	K607T	p.Lys607Thr	2048A>C	c.1820A>C	5.28×10^{-3}	2
10	T630I	p.Thr630Ile	2117C>T	c.1889C>T	1.21×10^{-7}	1
11	P655R	p.Pro655Arg	2192C>G	c.1964C>G	6.86×10^{-5}	1
11	D806H	p.Asp806His	2644G>C	c.2416G>C	8.00×10^{-5}	1
11	V894I	p.Val894Ile	2908G>A	c.2680G>A	8.36×10^{-6}	1
11	L929S	p.Leu929Ser	3014T>C	c.2786T>C	7.41×10^{-5}	1
11	D935N	p.Asp935Asn	3031G>A	c.2803G>A	5.29×10^{-7}	1
11	N987I	p.Asn987Ile	3188A>T	c.2960A>T	7.41×10^{-5}	1
11	L1019V	p.Leu1019Val	3283C>G	c.3055C>G	7.14×10^{-9}	1
11	N1102Y	p.Asn1102Tyr	3532A>T	c.3304A>T	8.30×10^{-5}	1
11	S1172L	p.Ser1172Leu	3743C>T	c.3515C>T	3.15×10^{-7}	1
11	R1190W	p.Arg1190Trp	3796C>T	c.3568C>T	1.09×10^{-8}	1
11	G1194D	p.Gly1194Asp	3809G>A	c.3581G>A	6.46×10^{-5}	1
11	N1228D	p.Asn1228Asp	3910A>G	c.3682A>G	5.48×10^{-6}	1
11	C1265S	p.Cys1265Ser	4021T>A	c.3793T>A	8.81×10^{-4}	1

11	D1280V	p.Asp1280Val	4067A>T	c.3839A>T	$2.86x10^{-5}$	1
11	V1306I	p.Val1306Ile	4144G>A	c.3916G>A	$6.85x10^{-6}$	1
11	I1349T	p.Ile1349Thr	4274T>C	c.4046T>C	$8.80x10^{-6}$	1
11	D1352Y	p.Asp1352Tyr	4282G>T	c.4054G>T	$4.14x10^{-2}$	2
11	T1354M	p.Thr1354Met	4289C>T	c.4061C>T	$8.03x10^{-5}$	1
11	C1365Y	p.Cys1365Tyr	4322G>A	c.4094G>A	$1.36x10^{-4}$	1
11	Q1396R	p.Gln1396Arg	4415A>G	c.4187A>G	$8.95x10^{-6}$	1
11	D1420Y	p.Asp1420Tyr	4486G>T	c.4258G>T	$1.02x10^{-4}$	1
11	K1434I	p.Lys1434Ile	4529A>T	c.4301A>T	$4.05x10^{-2}$	2
11	F1524V	p.Phe1524Val	4798T>G	c.4570T>G	$2.08x10^{-5}$	1
11	G1529R	p.Gly1529Arg	4813G>A	c.4585G>A	$1.66x10^{-10}$	1
11	K1690N	p.Lys1690Asn	5298A>C	c.5070A>C	$1.94x10^{-7}$	1
11	S1733F	p.Ser1733Phe	5426C>T	c.5198C>T	$1.53x10^{-10}$	1
11	S1760A	p.Ser1760Ala	5506T>G	c.5278T>G	$1.21x10^{-2}$	2
11	G1771D	p.Gly1771Asp	5540G>A	c.5312G>A	$1.53x10^{-7}$	1
11	P1819S	p.Pro1819Ser	5683C>T	c.5455C>T	$1.20x10^{-7}$	1
11	L1904V	p.Leu1904Val	5938C>G	c.5710C>G	$2.09x10^{-5}$	1
11	H1918Y	p.His1918Tyr	5980C>T	c.5752C>T	$5.75x10^{-6}$	1
11	I1929V	p.Ile1929Val	6013A>G	c.5785A>G	$5.21x10^{-6}$	1
11	R2034C	p.Arg2034Cys	6328C>T	c.6100C>T	$5.71x10^{-6}$	1
11	N2048I	p.Asn2048Ile	6371A>T	c.6143A>T	$3.19x10^{-5}$	1
11	H2074N	p.His2074Asn	6448C>A	c.6220C>A	$3.13x10^{-6}$	1
11	R2108H	p.Arg2108His	6551G>A	c.6323G>A	$3.72x10^{-13}$	1
11	N2113S	p.Asn2113Ser	6566A>G	c.6338A>G	$1.17x10^{-11}$	1
11	T2250A	p.Thr2250Ala	6976A>G	c.6748A>G	$2.03x10^{-5}$	1
11	G2274V	p.Gly2274Val	7049G>T	c.6821G>T	$1.17x10^{-2}$	2
12	I2285V	p.Ile2285Val	7081A>G	c.6853A>G	$2.60x10^{-10}$	1
12	D2312V	p.Asp2312Val	7163A>T	c.6935A>T	$5.43x10^{-7}$	1
13	R2318Q	p.Arg2318Gln	7181G>A	c.6953G>A	$2.65x10^{-3}$	2
14	A2351G	p.Ala2351Gly	7280C>G	c.7052C>G	$2.74x10^{-2}$	2
14	G2353R	p.Gly2353Arg	7285G>C	c.7513G>C	$6.12x10^{-4}$	1
14	Q2384K	p.Gln2384Lys	7378C>A	c.7150C>A	$3.34x10^{-7}$	1
14	L2396F	p.Leu2396Phe	7416G>T	c.7150C>A	$1.84x10^{-4}$	1
14	K2411T	p.Lys2411Thr	7460A>C	c.7232A>C	$2.60x10^{-4}$	1
14	R2418G	p.Arg2418Gly	7480A>G	c.7252A>G	$3.38x10^{-2}$	2
14	N2436I	p.Asn2436Ile	7535A>T	c.7307A>T	$2.34x10^{-4}$	1
14	K2446E	p.Lys2446Glu	7564A>G	c.7336A>G	$3.78x10^{-2}$	2
14	K2472T	p.Lys2472Thr	7643A>C	c.7415A>C	$1.63x10^{-7}$	1
15	T2515I	p.Thr2515Ile	7772C>T	c.7544C>T	$6.43x10^{-5}$	1
16	P2589H	p.Pro2589His	7994C>A	c.7766C>A	0.04	2
17	W2626C	p.Trp2626Cys	8106G>C	c.7878G>C	1.00	5
17	I2627F	p.Ile2627Phe	8107A>T	c.7879A>T	1.00	5
17	L2647P	p.Leu2647Pro	8168T>C	c.7940T>C	0.95	4
17	L2653P	p.Leu2653Pro	8186T>C	c.7958T>C	0.99	5
17	[a]R2659K	p.Arg2659Lys	8204G>A	c.7976G>A	1.00	5
18	[a]E2663V	p.Glu2663Val	8216A>T	c.7988A>T	1.00	5

18	D2665G	p.Asp2665Gly	8222A>G	c.7994A>G	$1.45x10^{-3}$	2
18	M2676T	p.Met2676Thr	8255T>C	c.8027T>C	0.03	2
18	A2717S	p.Ala2717Ser	8377G>T	c.8149G>T	$4.95x10^{-6}$	1
18	T2722R	p.Thr2722Arg	8393C>G	c.8165C>G	1.00	5
18	D2723H	p.Asp2723His	8395G>C	c.8167G>C	1.00	5
18	[a]D2723G	p.Asp2723Gly	8396A>G	c.8168A>G	0.99	5
18	K2729N	p.Lys2729Asn	8415G>T	c.8187G>T	$5.04x10^{-5}$	1
18	G2748D	p.Gly2748Asp	8471G>A	c.8243G>A	1.00	5
18	A2770T	p.Ala2770Thr	8536G>A	c.8308G>A	0.01	2
19	R2787H	p.Arg2787His	8588G>A	c.8360G>A	0.04	2
20	R2842H	p.Arg2842His	8753G>A	c.8525G>A	$2.59x10^{-4}$	1
20	E2856A	p.Glu2856Ala	8795A>C	c.8567A>C	$1.20x10^{-12}$	1
20	Q2858R	p.Gln2858Arg	8801A>G	c.8573A>G	0.02	2
21	R2888C	p.Arg2888Cys	8890C>T	c.8662C>T	$2.48x10^{-5}$	1
21	V2908G	p.Val2908Gly	8951T>G	c.8723T>G	$7.54x10^{-3}$	2
22	E2947K	p.Glu2947Lys	9067G>A	c.8839G>A	0.04	2
22	K2950N	p.Lys2950Asn	9078G>T	c.8850G>T	$8.14x10^{-3}$	2
22	D2965H	p.Asp2965His	9121G>C	c.8893G>C	0.03	2
22	V2969M	p.Val2969Met	9133G>A	c.8905G>A	$1.10x10^{-5}$	1
22	R2973C	p.Arg2973Cys	9145C>T	c.8917C>T	$5.44x10^{-6}$	1
24	R3052Q	p.Arg3052Gln	9383G>A	c.9155G>A	$5.45x10^{-3}$	2
24	R3052W	p.Arg3052Trp	9382C>T	c.9154C>T	1.00	5
24	P3063S	p.Pro3063Ser	9415C>T	c.9187C>T	0.02	2
24	V3079I	p.Val3079Ile	9463G>A	c.9235G>A	$2.00x10^{-5}$	1
25	Y3092C	p.Tyr3092Cys	9503A>G	c.9275A>G	0.03	2
25	D3095E	p.Asp3095Glu	9513C>G	c.9285C>G	0.98	4
25	Y3098H	p.Tyr3098His	9520T>C	c.9292T>C	$1.07x10^{-5}$	1
26	D3170G	p.Asp3170Gly	9737A>G	c.9509A>G	$2.64x10^{-5}$	1
26	C3198R	p.Cys3198Arg	9820T>C	c.9592T>C	$3.68x10^{-6}$	1
27	K3326X	p.Lys3326X	10204A>T	c.9976A>T	$2.04x10^{-9}$	1
27	T3349A	p.Thr3349Ala	10273A>G	c.10045A>G	$9.19x10^{-8}$	1

Table 4: Classification of BRCA1 and BRCA2 candidate splicing variants as class1, 2 or class 4, 5. Note that the numbering system for BRCA variants has evolved over time so the original terminology (BIC) and the newer terminology (HGVS) are shown side by side, as some individuals may have reports on file that use one or the other of these. The IARC class refers back to Table 1 in this article.

Gene	Exon	Codon	HGVS: DNA level	BIC: DNA level	Posterior probability of being deleterious	IARC class
BRCA1	3	IVS2-11delT	c.81-11delT	200-11delT	$4.62x10^{-5}$	1
BRCA1	3	IVS2-13C>G	c.81-13C>G	200-13C>G	$3.01x10^{-4}$	1
BRCA1	5	IVS5+3A>G	c.212+3A>G	331+3A>G	1.00	5
BRCA1	6	IVS6+7G>A	c.301+7G>A	420+7G>A	$6.27x10^{-5}$	1
BRCA1	7	IVS6-1G>C	c.302-1G>C	421-1G>C	1.00	5
BRCA1	7	IVS6-3C>G	c.302-3C>T	421-3C>G	0.99	5
BRCA1	9	IVS8-17G>T	c.548-17G>T	667-17G>T	$3.19x10^{-7}$	1
BRCA1	9	IVS9+4A>G	c.593+4A>G	712+4A>G	0.01	2
BRCA1	12	IVS11-1G>A	c.4097-1G>A	4216-1G>A	1.00	5
BRCA1	12	IVS11-11T>C	c.4097-11T>C	4216-11T>C	$5.42x10^{-4}$	1
BRCA1	12	IVS12+10G>C	c.4185+10G>C	4304+10G>C	$4.37x10^{-4}$	1
BRCA1	13	IVS13+1G>A	c.4357+1G>A	4476+1G>A	1.00	5
BRCA1	15	IVS15+1G>A	c.4675+1G>A	4794+1G>A	1.00	5
BRCA1	16	IVS15-7C>T	c.4676-7C>T	4795-7C>T	$2.80x10^{-3}$	2
BRCA1	17	IVS16-20A>G	c.4987-20A>G	5106-20A>G	$1.97x10^{-7}$	1
BRCA1	17	IVS17+1G>A	c.5074+1G>A	5193+1G>A	1.00	5
BRCA1	18	IVS17-9A>T	c.5075-9A>T	5194-9A>T	$1.61x10^{-3}$	2
BRCA1	18	IVS18+1G>T	c5152+1G>T	5271+1G>T	1.00	5
BRCA1	19	IVS18-13A>G	c.5153-13A>G	5272-13A>G	$5.17x10^{-5}$	1
BRCA1	19	IVS18-1G>C	c.5153-1G>C	5272-1G>C	1.00	5
BRCA1	19	IVS18-6C>A	c.5153-6C>A	5272-6C>A	$9.01x10^{-6}$	1
BRCA1	20	IVS19-12G>A	c.5194-12G>A	5313-12G>A	1.00	5
BRCA1	20	IVS20+1G>A	c.5277+1G>A	5396+1G>A	1.00	5
BRCA1	22	IVS21-8C>T	c.5333-8C>T	5452-8C>T	$1.12x10^{-3}$	2
BRCA1	23	IVS23+5G>C	c.5467+5G>C	5586G>C	0.04	2
BRCA2	6	IVS5-2A>G	c.476-2A>G	704-2A>G	1.00	5
BRCA2	6	IVS6+1G>T	c.516+1G>T	744+1G>T	0.96	4
BRCA2	9	IVS8-12delTA	c.791delTA	910-12delTA	$2.80x10^{-3}$	2
BRCA2	12	IVS11-20T>A	c.6842-20T>A	7070-20T>A	$2.73x10^{-4}$	1
BRCA2	13	IVS13+1G>C	c.7007+1G>C	7235+1G>C	0.98	4
BRCA2	15	IVS14-14T>G	c.7436-14T>G	7664G>C	$6.98x10^{-3}$	2
BRCA2	16	IVS15-1G>A	c.7618-1G>A	7846-1G>A	1.00	5
BRCA2	19	IVS19+1G>A	c.8487+1G>A	8715+1G>A	1.00	5
BRCA2	21	IVS20-16C>G	c.8633-16C>G	8861-16C>G	$2.12x10^{-3}$	2
BRCA2	21	IVS21+4A>G	c.8754+4A>G	8982+4A>G	0.93	4
BRCA2	22	IVS22+1G>T	c.8953+1G>T	9181+1G>T	1.00	5

BRCA2	23	P3039P	c.9117G>A	9345G>A	1.00	5
BRCA2	25	IVS24-1G>C	c.9257-1G>C	9485-1G>C	1.00	5
BRCA2	25	IVS25+9A>C	c.9501+9A>C	9729+9A>C	$2.26x10^{-4}$	1
BRCA2	27	IVS26-20C>T	c.9649-20C>T	9877-20C>T	$1.16x10^{-5}$	1

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