

Biological and clinical evidence for somatic mutations in *BRCA1* and *BRCA2* as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting

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Supplemental data

Supplemental Table 1. Mutation status for 209 Study 19 patients with tumor assay results. Each patient tumor has a tumor mutation classification (*BRCA1/2* loss-of-function mutation of germline, somatic, or unknown origin; VUS; or non-mutant), mutation type, amino acid change, predicted germline or somatic status, and predicted zygosity of mutations, compared with germline assay test type (CRF, Myriad, both, or not tested) and assay result (mutant, non-mutant, VUS, not tested)

Patient	Tumor <i>BRCA1</i> test				Tumor <i>BRCA2</i> test				Germline <i>BRCA1/2</i> test	
Classification	Mutation type	Amino acid change	Germline/somatic	Zygosity	Mutation type	Amino acid change	Germline/somatic	Zygosity	Germline assay test	Germline assay classification
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous					CRF	Mutant
<i>gBRCA1</i> m	Frameshift	E23fs*17	Germline	Homozygous					CRF	Mutant
<i>gBRCA1</i> m	Frameshift	E23fs*17	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift; VUS	V340fs*1; E575K	Germline; germline	Homozygous; homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous					CRF	Mutant
<i>gBRCA1</i> m	Nonsense	E418*	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1</i> m	Frameshift	E23fs*17	Germline	Homozygous					CRF	Mutant
<i>gBRCA1</i> m	Nonsense	Y978*	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous					Not tested	Not tested
<i>gBRCA1</i> m	Frameshift	S1655fs*16	Germline	Homozygous					CRF	Mutant
<i>gBRCA1</i> m (+ VUS)	Frameshift	Q1756fs*74	Germline	Homozygous	VUS	P1819S	Germline	Heterozygous	Both	Mutant

<i>gBRCA1m</i>	Frameshift	T826fs*20	Germline	Homozygous					Both	Mutant
<i>gBRCA1m</i>	Frameshift	E23fs*17	Germline	Homozygous					Both	Mutant
<i>gBRCA1m</i>	Frameshift	Q1756fs*74	Germline	Homozygous					Not tested	Not tested
<i>gBRCA1m</i>	Frameshift	Q1756fs*74	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1m</i>	Frameshift	E23fs*17	Germline	Homozygous					CRF	Mutant
<i>gBRCA1m</i>	Frameshift	E23fs*17	Germline	Homozygous					CRF	Mutant
<i>gBRCA1m</i>	Nonsense	R1203*	Germline	Homozygous					Not tested	Not tested
<i>gBRCA1m</i> (+ VUS)	Frameshift	R136fs*27	Germline	Homozygous	VUS; VUS	M3162I; I1188M	Germline; germline	Tumor; not in tumor	Both	Mutant
<i>gBRCA1m</i>	Frameshift	Q1756fs*74	Germline	Homozygous					Both	Mutant
<i>gBRCA1m</i>	Nonsense	R1203*	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1m</i> (+ VUS)	Frameshift; VUS	E23fs*17; M658I	Germline; germline	Homozygous; not in tumor					Both	Mutant
<i>gBRCA1m</i> (+ VUS)	Frameshift	Q1756fs*74	Germline	Homozygous	VUS	S1172L	Germline	Heterozygous	Both	Mutant
<i>gBRCA1m</i> (+ VUS)	Frameshift	K654fs*47	Germline	Homozygous	VUS	S384F	Germline	Heterozygous	CRF	Mutant
<i>gBRCA1m</i>	Nonsense	Q74*	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1m</i>	Frameshift	P1238fs*26	Germline	Homozygous					Not tested	Not tested
<i>gBRCA1m</i>	Frameshift	E23fs*17	Germline	Homozygous					Both	Mutant
<i>gBRCA1m</i>	Frameshift	Q1756fs*74	Germline	Homozygous					Myriad	Non-mutant

<i>gBRCA1</i> m	Nonsense	E1250*	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift	V1234fs*8	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1</i> m	Frameshift	S1253fs*10	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift	A807fs*8	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift	E23fs*17	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m (+ VUS)	Frameshift	S282fs*15	Germline	Homozygous	VUS	M1149T	Germline	Heterozygous	CRF	Mutant
<i>gBRCA1</i> m (+ VUS)	Frameshift; VUS; VUS	Q1756fs*74; Q1227H; D411V	Germline; germline; germline	Homozygous; not in tumor; not in tumor					CRF	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous					Myriad	Non-mutant
<i>gBRCA1</i> m (+ VUS)	Frameshift; VUS	E765fs*1; G535R	Germline; germline	Homozygous; homozygous					Not tested	Not tested
<i>gBRCA1</i> m (+ VUS)	Nonsense; VUS	R1203*; L246V	Germline; germline	Homozygous; homozygous					Myriad	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m	Frameshift	D1065fs*2	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1</i> m	Nonsense	R1203*	Germline	Homozygous					Myriad	Mutant
<i>gBRCA1</i> m (+ VUS)	Frameshift; VUS	Q1756fs*74; S590G	Germline; germline	Homozygous; homozygous					Not tested	Not tested

<i>gBRCA1</i> m	Frameshift	E23fs*17	Germline	Homozygous	CRF	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Homozygous	Not tested	Not tested
<i>gBRCA1</i> m	Nonsense	Q780*	Germline	Unknown	Both	Mutant
<i>gBRCA1</i> m	Frameshift	S945fs*6	Germline	Unknown	Not tested	Not tested
<i>gBRCA1</i> m	Frameshift	R1835fs*10+	Germline	Unknown	Both	Mutant
<i>gBRCA1</i> m	Frameshift	E23fs*17	Germline	Unknown	CRF	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Unknown	Myriad	Mutant
<i>gBRCA1</i> m	Nonsense	E908*	Germline	Unknown	Both	Mutant
<i>gBRCA1</i> m	Frameshift	P1806fs*28	Germline	Unknown	Myriad	Mutant
<i>gBRCA1</i> m	Frameshift	M1083fs*1	Germline	Unknown	Myriad	Mutant
<i>gBRCA1</i> m	Nonsense	R1443*	Germline	Unknown	CRF	Mutant
<i>gBRCA1</i> m	Frameshift	S1428fs*6	Germline	Unknown	Both	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Unknown	Myriad	Mutant
<i>gBRCA1</i> m	Frameshift	Q1756fs*74	Germline	Unknown	Both	Mutant
<i>sBRCA1</i> m	Nonsense	R1203*	Somatic	Homozygous	CRF	Non-mutant
<i>sBRCA1</i> m	Frameshift	I600fs*7	Somatic	Homozygous	Myriad	Non-mutant
<i>sBRCA1</i> m	Frameshift	S1486fs*19	Somatic	Homozygous	Myriad	Non-mutant
<i>sBRCA1</i> m	Frameshift	N542fs*2	Somatic	Homozygous	Myriad	Non-mutant
<i>sBRCA1</i> m	Frameshift	L1472fs*33	Somatic	Homozygous	Not tested	Not tested
<i>sBRCA1</i> m	Frameshift	K50fs*19	Somatic	Homozygous	Myriad	Non-mutant
<i>sBRCA1</i> m	Nonsense	E1629*	Somatic	Homozygous	Myriad	Non-mutant

<i>sBRCA1</i> m	Nonsense	Q1327*	Somatic	Homozygous					Myriad	Non-mutant
(<i>s</i>) <i>BRCA1</i> m	Frameshift	N1355fs*10	NA	Unknown					Myriad	Non-mutant
<i>gBRCA1</i> m	Splice	Splice	Germline	Homozygous					Both	Mutant
<i>sBRCA1</i> m	Splice	Splice	Somatic	Homozygous					Not tested	Not tested
<i>sBRCA1</i> m	Splice	Splice	Somatic	Homozygous					Not tested	Not tested
(<i>g</i>) <i>BRCA1</i> m	Deletion	0 copies							CRF	Mutant
<i>gBRCA1</i> m	Known-missense	R1699Q	Germline	Homozygous					Both	Mutant
<i>gBRCA1</i> m (+ VUS)	Known-missense	C61G	Germline	Homozygous	VUS	L1195M	Germline	Homozygous	Myriad	Mutant
<i>gBRCA1</i> m	Known-missense	A1708E	Germline	Homozygous					CRF	Non-mutant
<i>gBRCA1</i> m	Known-missense	R1699W	Germline	Homozygous					Both	Mutant
<i>sBRCA1</i> m	Known-missense	M1T	Somatic	Homozygous					Myriad	Non-mutant
<i>gBRCA2</i> m (+ VUS)	VUS	P1238L	Germline	Homozygous	Frameshift; VUS	S599fs*1; K1690N	Germline; germline	Homozygous; homozygous	CRF	Non-mutant
<i>gBRCA2</i> m					Frameshift	A938fs*21	Germline	Homozygous	Myriad	Non-mutant
<i>gBRCA2</i> m					Nonsense	S1882*	Germline	Homozygous	Myriad	Mutant
<i>gBRCA2</i> m					Frameshift;	V1610fs*4;	Germline	Homozygous;	Not tested	Not tested

(+ VUS)					VUS	splice		not in tumor		
<i>gBRCA2m</i>					Frameshift	L1466fs*2	Germline	Homozygous	Not tested	Not tested
<i>gBRCA2m</i>					Frameshift	E1493fs*10	Germline	Homozygous	Myriad	Mutant
<i>gBRCA2m</i>					Frameshift	S1982fs*22	Germline	Homozygous	CRF	Mutant
<i>gBRCA2m</i>					Frameshift	W1692fs*3	Germline	Homozygous	Both	Mutant
<i>gBRCA2m</i>					Frameshift	V1283fs*2	Germline	Homozygous	Myriad	Mutant
<i>gBRCA2m</i>					Frameshift	F2254fs*6	Germline	Homozygous	Not tested	Not tested
<i>gBRCA2m</i>	VUS	L440S	Germline	Homozygous	Nonsense	R3128*	Germline	Homozygous	Both	Mutant
(+ VUS)										
<i>gBRCA2m</i>					Frameshift	V1610fs*4	Germline	Homozygous	CRF	Non-mutant
<i>gBRCA2m</i>					Frameshift	S1982fs*22	Germline	Homozygous	CRF	Mutant
<i>gBRCA2m</i>					Frameshift;	V1283fs*2;	Germline;	Homozygous;	Myriad	Mutant
(+ VUS)					VUS	I2672V	germline	not in tumor		
<i>gBRCA2m</i>					Frameshift	Q2009fs*9	Germline	Homozygous	CRF	Mutant
<i>gBRCA2m</i>					Frameshift	N1544fs*4	Germline	Homozygous	Myriad	Mutant
<i>gBRCA2m</i>					Nonsense	L1118_E11 19>*	Germline	Homozygous	Myriad	Mutant
<i>gBRCA2m</i>					Frameshift	V1804fs*2	Germline	Homozygous	CRF	Mutant
<i>gBRCA2m</i>					Frameshift	Q1175fs*7	Germline	Homozygous	Not tested	Not tested
<i>gBRCA2m</i>					Frameshift	S1982fs*22	Germline	Homozygous	Both	Mutant
<i>gBRCA2m</i>					Frameshift	E1646fs*24	Germline	Homozygous	Myriad	Mutant

<i>gBRCA2m</i>					Frameshift	L2092fs*7	Germline	Unknown	Not tested	Not tested
<i>gBRCA2m</i>					Frameshift	S1982fs*22	Germline	Unknown	CRF	Mutant
<i>gBRCA2m</i>					Frameshift	E1646fs*24	Germline	Unknown	Both	Mutant
<i>gBRCA2m</i>					Nonsense	R2494*	Germline	Unknown	Myriad	Mutant
<i>gBRCA2m</i>					Frameshift	R645fs*15	Germline	Unknown	CRF	Mutant
<i>sBRCA2m</i>					Frameshift	W31fs*1	Somatic	Homozygous	CRF	Non-mutant
<i>sBRCA2m</i> (+ VUS)					Nonsense; VUS	K2939*; Y3098H	Somatic; germline	Homozygous; not in tumor	Not tested	Not tested
<i>sBRCA2m</i>					Frameshift	D1321fs*14	Somatic	Homozygous	CRF	Non-mutant
<i>sBRCA2m</i>					Frameshift	D2005fs*34	Somatic	Homozygous	CRF	Non-mutant
<i>sBRCA2m</i>					Frameshift	L2996fs*5	Somatic	Heterozygous	CRF	Non-mutant
<i>sBRCA2m</i>					Frameshift	L2587fs*9	Subclonal somatic	Unknown	Not tested	Not tested
<i>sBRCA2m</i> (+ VUS)	VUS	T826K	Germline	Homozygous	Frameshift	T2515fs*9	Subclonal somatic	Unknown	Not tested	Not tested
(s) <i>BRCA2m</i>					Deletion	0 copies			Myriad	Non-mutant
(g) <i>BRCA2m</i>					Deletion	0 copies			Myriad	Mutant
<i>uBRCA2m</i>					Deletion	0 copies			Not tested	Not tested
(<i>gBRCA</i> ; FM tumor no call)	(Insertion)								CRF	Mutant
(<i>gBRCA</i> ; FM)	(Insertion)								Myriad	Mutant

tumor no call) (gBRCA; FM tumor no call)	(Deletion)								CRF	Mutant
VUS-LOH	VUS	T1700I	Germline	Homozygous					Myriad	VUS
VUS-LOH					VUS	N2113S	Germline	Homozygous	CRF	Non-mutant
VUS-LOH					VUS	D2679Y	Germline	Homozygous	Myriad	VUS
VUS-LOH	VUS	E649Q	Germline	Homozygous					Myriad	VUS
VUS-LOH					VUS	K607T	Germline	Homozygous	Not tested	Not tested
VUS-NA	VUS	Q804H	Germline	Unknown					Myriad	Non-mutant
VUS-NA	VUS	R504C	Germline	Unknown					Both	Non-mutant
VUS-NA (two somatic)					VUS; VUS	E2260Q; E2275K	Somatic; somatic	Unknown; unknown	CRF	Non-mutant
VUS-HET					VUS	D125G	Germline	Heterozygous	Not tested	Not tested
VUS-NIT					VUS	N54I	Germline	Not in tumor	Both	Non-mutant
VUS-NIT	VUS	V1714_S171 5del	Germline	Not in tumor					Myriad	Non-mutant
VUS-NIT	VUS	N799K	Germline	Not in tumor					Myriad	VUS
Non-mutant (S236R SNP)					Non-mutant VUS	S326R	Germline	Not in tumor	Myriad	Non-mutant
Non-mutant									Myriad	Non-mutant
Non-mutant									Both	Non-mutant

Non-mutant		Not tested	Not tested
Non-mutant		Not tested	Not tested
Non-mutant		CRF	Non-mutant
Non-mutant		CRF	Non-mutant
Non-mutant		CRF	Non-mutant
Non-mutant		Both	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Not tested	Not tested
Non-mutant		Not tested	Not tested
Non-mutant		Not tested	Not tested
Non-mutant		Not tested	Not tested
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Both	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant

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Not tested	Not tested
Myriad	Non-mutant
Not tested	Not tested
Myriad	Non-mutant
Both	Non-mutant
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Myriad	Non-mutant
Myriad	Non-mutant
Both	Non-mutant
Both	Non-mutant
Myriad	Non-mutant
Both	Non-mutant
CRF	Non-mutant
Not tested	Not tested
Myriad	Non-mutant
Myriad	Non-mutant
Myriad	Non-mutant
Myriad	Non-mutant
Not tested	Not tested
Myriad	Non-mutant
Not tested	Not tested

Non-mutant		Myriad	Non-mutant
Non-mutant		Both	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Both	Non-mutant
Non-mutant		Both	Non-mutant
Non-mutant		Not tested	Not tested
Non-mutant		Myriad	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Not tested	Not tested
Non-mutant		Myriad	Non-mutant
Non-mutant		CRF	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Both	Non-mutant
Non-mutant		Myriad	Non-mutant
Non-mutant		Not tested	Not tested
Non-mutant		Myriad	Non-mutant

CRF, case report form; FM, Foundation medicine; *gBRCAm*, germline *BRCA* mutation; HET, heterozygous; LOH, loss of heterozygosity; NA, not available; NIT, not in tumor; *sBRCAm*, somatic *BRCA* mutation; SNP, single nucleotide polymorphism; VUS, variant of unknown significance

Supplemental Table 2. Comparison of *BRCA1/2* mutations for Study 19 with three published cohorts of high-grade serous ovarian cancer patients [1-3]. Number of patients sequenced, origin of *BRCA1/2* mutation (germline, somatic, or unknown), frequencies of *BRCA1/2* mutation, and somatic mutation rates are presented. Some data for Hennessey et al. [4] are not presented here owing to testing of a subset of samples for germline and somatic status

	Study 19	Pennington 2014 [2]	TCGA 2011 [1]	Hennessey 2010 [4]
HG-SOC patients sequenced, n	209	249	316	158
<i>BRCA1/2</i> m, n	114	65	63	36
Germline	93	53	44 ^a	N/A
Somatic	20	12	19	N/A
Unknown	1	0	0	N/A
<i>BRC</i> Am, %	55	26	20	23
s <i>BRC</i> Am, %	18	18	30	39 ^b

^aSubtracted three reported germline mutations (*BRCA2* K3326X is a benign polymorphism); ^bRepresents 11 somatic mutations in a subset of 28 *BRCA1/2*-mutated patients tested with no grade or histology stated.

HG-SOC, high-grade serous ovarian cancer; N/A, not available; TCGA, The Cancer Genome Atlas

References

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