Supplementary Methods

Variant Calling, Quality Control and Annotation Pipeline used to analyze the anonymized subset of the cohort.

Reads were aligned in paired-end mode to the hg19/b37 version of the human genome using BWA-MEM (Burrows-Wheeler Aligner) (1-3). Aligned reads were written to a Sequence Alignment Map (SAM) file, which was then converted into Binary Alignment Map (BAM) format using tools available in Picard (http://broadinstitute.github.io/picard/) (4). PCR duplicates were marked for exclusion in subsequent analysis stages using the MarkDuplicates tool in Picard. ABRA, a local aligner, was used to perform a local multiple sequence realignment of reads and remove artefactual SNPs in regions marked with an indel event (5). GATK (Genome Analysis Toolkit) BaseRecalibrator was used to adjust the reported quality scores based on the following covariates: read group, reported quality score, cycle and local sequence context (6). Reassigned quality scores were subject to a threshold of 20. GATK HaplotypeCaller (HTC) was used to call SNVs and Indels simultaneously from the read data. Joint calling was applied to all samples in the anonymized subset of the cohort so as to gather the best joint probabilities for each variant called in the data (7). Samples in this subset of the cohort were anonymized before any variant was annotated, according to the anonymization protocol described below. Subsequent processing of the variants including assigning annotations, QC and filtering based off annotations were then performed.

Quality Control/Quality Assurance (QC/QA)

QC/QA consisted of several steps. The multi-allelic variants (those with more than one alternate allele) were split to individual variants, and each variant was left aligned, =such that a parsimonious representation of the alternate allele was maintained. The genotypes with Depth (DP) <20, genotype quality (GQ) GQ<20, Allele Balance (AB) <20% and >80% for heterozygous and AB<80% for homozygous alternative alleles were turned to reference calls. Every variant with at least 10% or more genotypes that underwent changes was removed. The variants with fractions of missing genotypes over 10% were removed. Finally, variants corresponding to known systematic artifacts were removed from the data. QA was done by checking variants for mapping to known genes, performing allele frequency tests for departures from large population frequencies and excess homozygous alleles.

Annotation

VCF files were annotated with public annotators including CAVA, SNPEff, Annovar, ClinVar and public allele frequencies from large sequencing studies like ExAC (without cancer samples from TCGA) and gNOMAD (8-12). Variants with multiple transcripts were prioritized based on their impact using in-house code, and transcript IDs were on par with ClinVar representations.

Anonymization Protocol

For the anonymized subset of the cohort, clinically annotated data was binned, so that no database field contained a unique value and at least 2 individuals remain in any distinct identifiable bin. The BAM files were identified using the BAM labels, temporarily linked by their clinical identifiers. The selected BAMs were then processed as described above, and variants were called. At this stage, a unique set of random alphanumeric values was assigned to each sample. The same alpha-numerics were also used to replace both the unique clinical identifier in the clinical data file as well as in the variant data file VCF. Finally, any files that carried the original identifiers were destroyed, such that the samples were fully anonymized and could not be linked back to any clinical identifiers.

REFERENCES

1. Li H, Durbin R. Fast and accurate long-read alignment with Burrows-Wheeler transform. *Bioinformatics*. 2010;26(5):589-95.
2. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics*. 2009;25(14):1754-60.
3. Ziemann M. Accuracy, speed and error tolerance of short DNA sequence aligners. bioRxiv. 2016.
4. Li H, Handsaker B, Wysoker A, et al. The Sequence Alignment/Map format and SAMtools. *Bioinformatics*. 2009;25(16):2078-9.
5. Yucel M, Aras B, Yalcinkaya S, et al. Conventional monopolar transurethral resection of prostate in patients with large prostate (>/=80 grams). *Cent European J Urol*. 2013;66(3):303-8.
6. DePristo MA, Banks E, Poplin R, et al. A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nat Genet*. 2011;43(5):491-8.
7. Hart SN, Maxwell KN, Thomas T, et al. Collaborative science in the next-generation sequencing era: a viewpoint on how to combine exome sequencing data across sites to identify novel disease susceptibility genes. *Brief Bioinform*. 2016;17(4):672-7.
8. Munz M, Ruark E, Renwick A, et al. CSN and CAVA: variant annotation tools for rapid, robust next-generation sequencing analysis in the clinical setting. *Genome Med*. 2015;7:76.
9. Cingolani P, Platts A, Wang le L, et al. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila melanogaster strain w1118; iso-2; iso-3. *Fly (Austin)*. 2012;6(2):80-92.
10. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res.* 2010;38(16):e164.
11. Landrum MJ, Lee JM, Riley GR, et al. ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res.* 2014;42. (Database issue)
12. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536(7616):285-91.

Supplementary Table 1: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets 76 Gene Panel

	Genes	Disease/Syndromes
1	ALK	Familial neuroblastoma
2	APC	Familial adenomatous polyposis
3	ATM	Ataxia-telangiectasia; ATM-related cancer risk
4	BAP1	Mesothelioma, uveal melanoma
5	BARD1	Hereditary breast and ovarian cancer syndrome
6	BLM	Bloom syndrome
7	BMPR1A	Juvenile polyposis syndrome
8	BRCA1	Hereditary breast and ovarian cancer syndrome
9	BRCA2	Hereditary breast and ovarian cancer syndrome; Fanconi anemia
10	BRIP1	BRIP1-related cancer; Fanconi anemia
11	CDH1	Hereditary diffuse gastric cancer
12	CDK4	Familial cutaneous melanoma
13	CDKN2A	Familial cutaneous melanoma
14	CHEK2	CHEK2-related cancer
15	DICER1	DICER1-Related Disorders.
16	EGFR	Familial lung cancer
17	EPCAM	Lynch syndrome
18	FAM175A (ABRAXIS)	Hereditary breast cancer syndrome
19	FH	Hereditary Leiomyomatosis and Renal Cell Cancer
20	FLCN	Birt-Hogg-Dubé syndrome
21	GATA2	Familial MDS-AML
22	GREM1	Hereditary mixed polyposis syndrome (HMPS)
23	HRAS	Costello syndrome
24	JAK2	Familial thrombocytosis
25	KIT	Hereditary Gastrointestinal stromal tumors (GISTs)
26	KRAS	Noonan Syndrome
27	MAX	Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes
28	MEN1	Multiple endocrine neoplasia, type 1
29	MET	Hereditary papillary renal carcinoma
30	MITF	Familial melanoma and renal cell carcinoma
31	MLH1	Lynch syndrome
32	MRE11A	Ataxia-telangiectasia-like disorder (recessive); breast cancer
33	MSH2	Lynch syndrome
34	MSH6	Lynch syndrome
35	MUTYH	MUTYH-associated polyposis (MAP)
36	NBN	Nijmegen breakage syndrome; NBN-related cancer risk
37	NF1	Neurofibromatosis, type 1
38	NF2	Neurofibromatosis, type 2
39	NRAS	Autoimmune lymphoproliferative syndrome (ALPS)
40	PALB2	PALB2-related cancer; Fanconi anemia
41	PAX5	B cell precursor acute lymphoblastic leukemia (B-ALL)

42	PDGFRA	Hereditary Gastrointestinal stromal tumors (GISTs)
43	PHOX2B	Familial neuroblastoma; Congenital central hypoventilation syndrome (CCHS)
44	PMS2	Lynch syndrome
45	POLE	Colorectal cancer and Endometrial cancer
46	PTCH1	Nevoid basal cell carcinoma syndrome (NBCCS)
47	PTEN	PTEN hamartoma tumor syndrome
48	RAD50	Nijmegen breakage syndrome-like disorder
49	RAD51	Hereditary breast cancer
50	RAD51B	Hereditary breast cancer
51	RAD51C	RAD51C-related cancer; Fanconi anemia
52	RAD51D	Hereditary ovarian cancer
53	RB1	Retinoblastoma
54	RECQL4	Rothmund-Thomson syndrome (RTS)
55	RET	Multiple endocrine neoplasia, type 2
56	RUNX1	Familial platelet disorder with predisposition to acute myelogenous leukaemia
57	SDHA	Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes
58	SDHAF2	Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes
59	SDHB	Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes
60	SDHC	Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes
61	SDHD	Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes
62	SMAD3	Thoracic aortic aneurysms and aortic dissections (TAAD)
63	SMAD4	Juvenile polyposis syndrome
64	SMARCA4	Rhabdoid tumor predisposition syndrome type 2
65	SMARCB1	Rhabdoid tumor predisposition syndrome type 1
66	STK11	Peutz-Jeghers syndrome
67	SUFU	Medulloblastoma
68	TERT	Familial pulmonary fibrosis (FPF); Dyskeratosis congenita (DC)
69	TGFBR1	Thoracic aortic aneurysms and aortic dissections (TAAD)
70	TGFBR2	Thoracic aortic aneurysms and aortic dissections (TAAD)
71	TMEM127	Familial pheochromocytoma syndrome
72	TP53	Li-Fraumeni syndrome
73	TSC1	Tuberous sclerosis complex (TSC)
74	TSC2	Tuberous sclerosis complex (TSC)
75	VHL	Von Hippel-Lindau syndrome; Familial erythrocytosis, type 2
76	WT1	WAGR (Wilms tumor-aniridia-genital anomalies-retardation) syndrome, Denys-Drash syndrome (DDS), Frasier syndrome, and isolated Wilms tumor

Supplementary Table 2: Demographics and Clinical Characteristics of Identified *BRCA* Patients*

Clinical Characteristics	**N=32**	**BRCA1 N=10**	**BRCA2 N= 22**
Age at diagnosis (years)			
< 40	3 (9.3%)	2 (66.7%)	1 (33.3%)
40-50	6 (18.8%)	2 (33.3%)	4 (66.7%)
51-60	9 (28.1%)	4 (44.4%)	5 (55.6%)
61-70	9 (28.1%)	2 (20.0%)	7 (80.0%)
71-80	5 (15.6%)	—	5 (100.0%)
>80	—	—	—
Median age at diagnosis (years)	59	54	60
Sex			
Male	19 (59.4%)	7 (36.8%)	12 (63.2%)
Female	13 (40.6%)	3 (23.2%)	10 (76.8%)
Race			
White	29 (90.6%)	10 (34.5%)	19 (65.5%)
Non-Ashkenazi Jewish	14 (48.3%)	5 (35.7%)	9 (64.3%)
Ashkenazi Jewish	15 (51.7%)	5 (33.3%)	10 (66.7%)
Black / Hispanic / Latino	3 (9.4%)	—	3 (100.0%)
Asian	—	—	—
Diabetes			
Yes	5 (15.6%)	—	5 (100.0%)
No	27 (84.4%	10 (35.7%)	17 (60.7%)
Smoking Status			
Yes	13 (40.6%)	—	13 (100.0%)
No	19 (59.4%)	10 (52.6%)	9 (47.4%)
Pathology			
Adenocarcinoma	30 (93.8%)	9 (30.0%)	21 (70.0%)
Adenosquamous carcinoma	1 (3.1%)	—	1 (100.0%)
Acinar cell carcinoma of the pancreas	1 (3.1%)	1 (100.0%)	—
Undifferentiated	—	—	—
MCN/ITPN/MPAC/IPMN/COLLOID/SPNP†	—	—	—

*—denotes 0

† (MCN) Mucinous Cystic Neoplasm, (ITPN) Intraductal Tubullopapillary Neoplasm, (MPAC) Mixed pancreatic and Acinar Cell Carcinoma of the Pancreas, (IPMN) Intra-Papillary Mucinous Neoplasm, (COLLOID) Colloid Intraductal Papillary Mucinous Neoplasm, (SPNP) Solid Pseudopapillary Neoplasm of the Pancreas

Supplementary Table 3: Specific Mutations, Founder Status, Clinical Details and Guidelines Met in *BRCA* Patients

Gene	Sex, Median Age at Diagnosis (range)	N=	Founder mutation	1st/2nd degree with cancer	Guidelines Met*	Stage at Diagnosis
BRCA1 (n=10)	M:F 7:3 64 yrs (32-68)					
c.427G>T (p.Glu143*)		1	N	Breast, PDAC	HBOC	IV
c.4986+5G>A		1	N	PDAC	HBOC	III
c.5266dupC (p.Gln1756Profs*74)		2	Y	PDAC, breast, ovary	HBOC (2/2 patients), LS (1/2 patients), FPC (1/2 patients)	IV, IV
c.65T>C (p.Leu22Ser)		1	N	Ovary, prostate	HBOC	IV
c.4524G>A (p.Trp1508*)		1	N	Breast	HBOC	IIB
c.68_69delAG (p.Glu23Valfs*17)		3	Y	Colon, breast, stomach	HBOC (3/3 patients)	IIB, IV, IV
c.181T>G (p.Cys61Gly)		1	Y	Laryngeal	HBOC	IV
BRCA2 (n=18)	M:F 9:9 60 yrs (37-77)					
c.5946delT (p.Ser1982Argfs*22)		9	Y	Breast , ovary, CRC	HBOC (9/9 patients), FPC (2/9 patients)	IV (6), IIB (2), IIA (1)
c.4829_4830delTG (p.Val1610Glyfs*4)		1	N	Tonsil, endometrial	N	IIA
c.5569delG (p.Glu1857Lysfs*6)		1	N	HCC, PDAC	N	IV
c.4638delT (p.Phe1546Leufs*22)		1	N	Melanoma	N	IV
c.793+1G>A		1	N	Breast, CRC	LS	IIB
c.9371A>T (p.Asn3124Ile)		1	Y	Breast	HBOC	IV
c.5614A>T (p.Lys1872*)		1	N	Breast	HBOC	IV
c.6259delA (p.Arg2087Glufs*32)		1	N	Breast	HBOC	IV
c.3847_3848del (p.Val1283Lysfs*2)		1	N	Gastric	HBOC	IIA

c.3264dupT (p.Gln1089Serfs*10)		1	N	Breast	HBOC	IV
Gene	**Sex, Age at Diagnosis**	**N=**	**Founder mutation**	**1st/2nd degree with cancer**	**Guidelines Met***	**Stage at Diagnosis**
BRCA2 + CHEK2 - c.5946delT (p.Ser1982Argfs*22) + c.1283C>T (p.Ser428Phe)	50, M	1	Y	Prostate, Breast, Gastric	HBOC	IV
BRCA2 + CHEK2 - c.9148C>T (p.Gln3050*) + c.1283C>T (p.Ser428Phe)	60, F	1	N	Breast	HBOC	IIA
BRCA2 + APC - c.5946delT (p.Ser1982Argfs*22) + c.3920T>A (p.Ile1307Lys)	64,M	1	N	Breast, PDAC, Cervical, Ovarian, Lung	HBOC, FPC, LS	IV
BRCA2 + PMS2 - c.6468_6469del (p.Gln2157Ilefs*18) + c.1831delinsTT (p.Ile611Phefs*2)	74, M	1	Y	Bladder, Lymphoma, Testicular	N	IIA

* NCCN: The National Comprehensive Cancer Network, HBOC: Hereditary Breast Ovary Cancer, ACMG: American College of Medical Genetics and Genomics, FPC: Familial Pancreatic Cancer, LS: Lynch Syndrome

Supplementary Table 4: Pathogenic Germline Alteration Screening Guidelines Met by *BRCA* Patients*

Guidelines Met (NCCN HBOC, ACMG: HBOC, Pancreatic, LS, FAMM) †			**Total**
	BRCA 1	**BRCA 2**	
0	—	5 (22.7%)	5 (15.6%)
1	2 (20.0%)	3 (13.6%)	5 (15.6%)
2	6 (60.0%)	9 (40.9%)	15 (46.9%)
3	2 (20.0%)	4 (18.2)	6 (18.8%)
4	—	1 (4.6%)	1 (3.1%)
5	—	—	—
Total	**10**	**22**	**32**

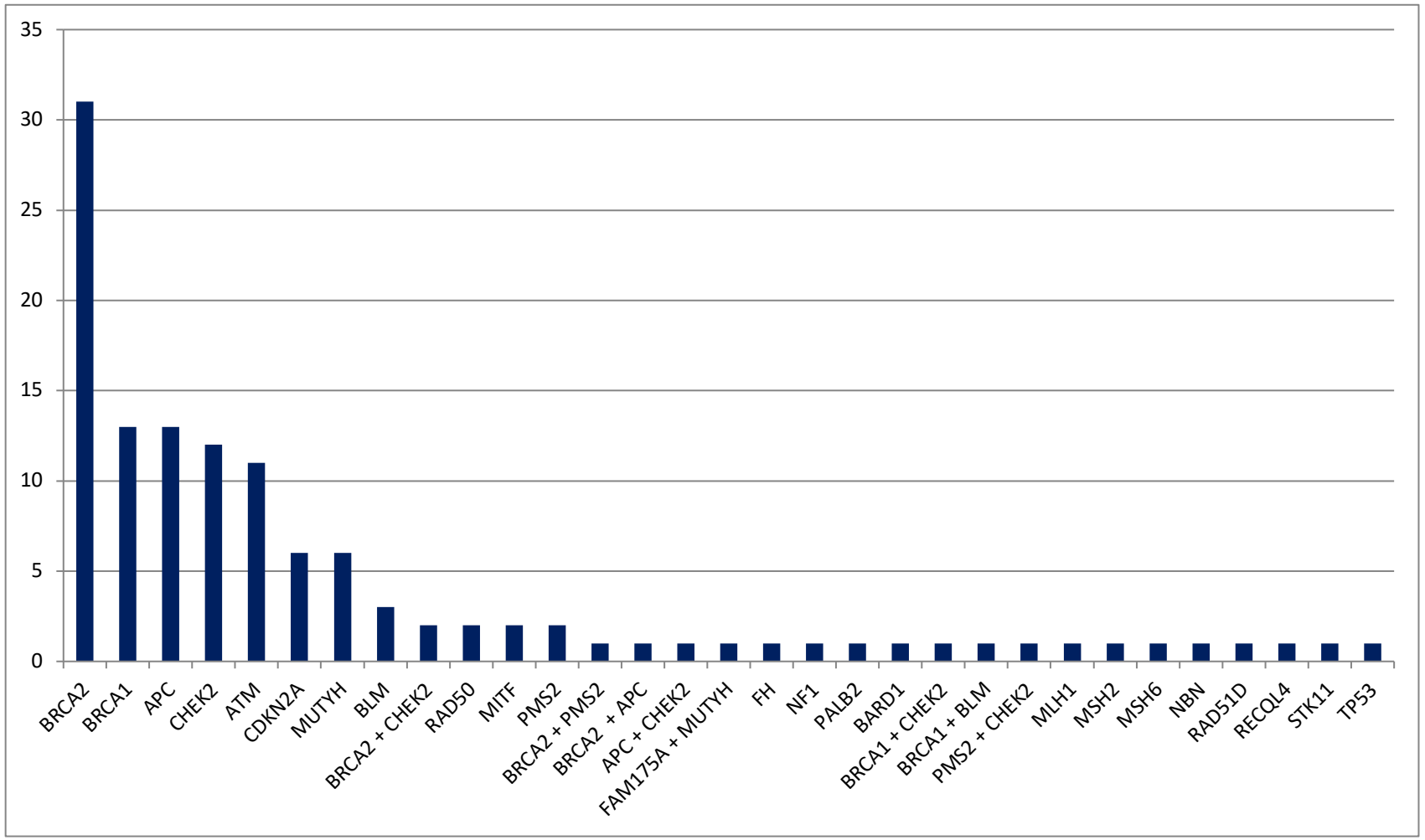
*—denotes 0

†NCCN: The National Comprehensive Cancer Network, HBOC: Hereditary Breast Ovary Cancer, ACMG: American College of Medical Genetics and Genomics, Pancreatic: Familial Pancreatic Cancer, LS: Lynch Syndrome, FAMM: Familial Atypical Multiple Mole Melanoma Syndrome

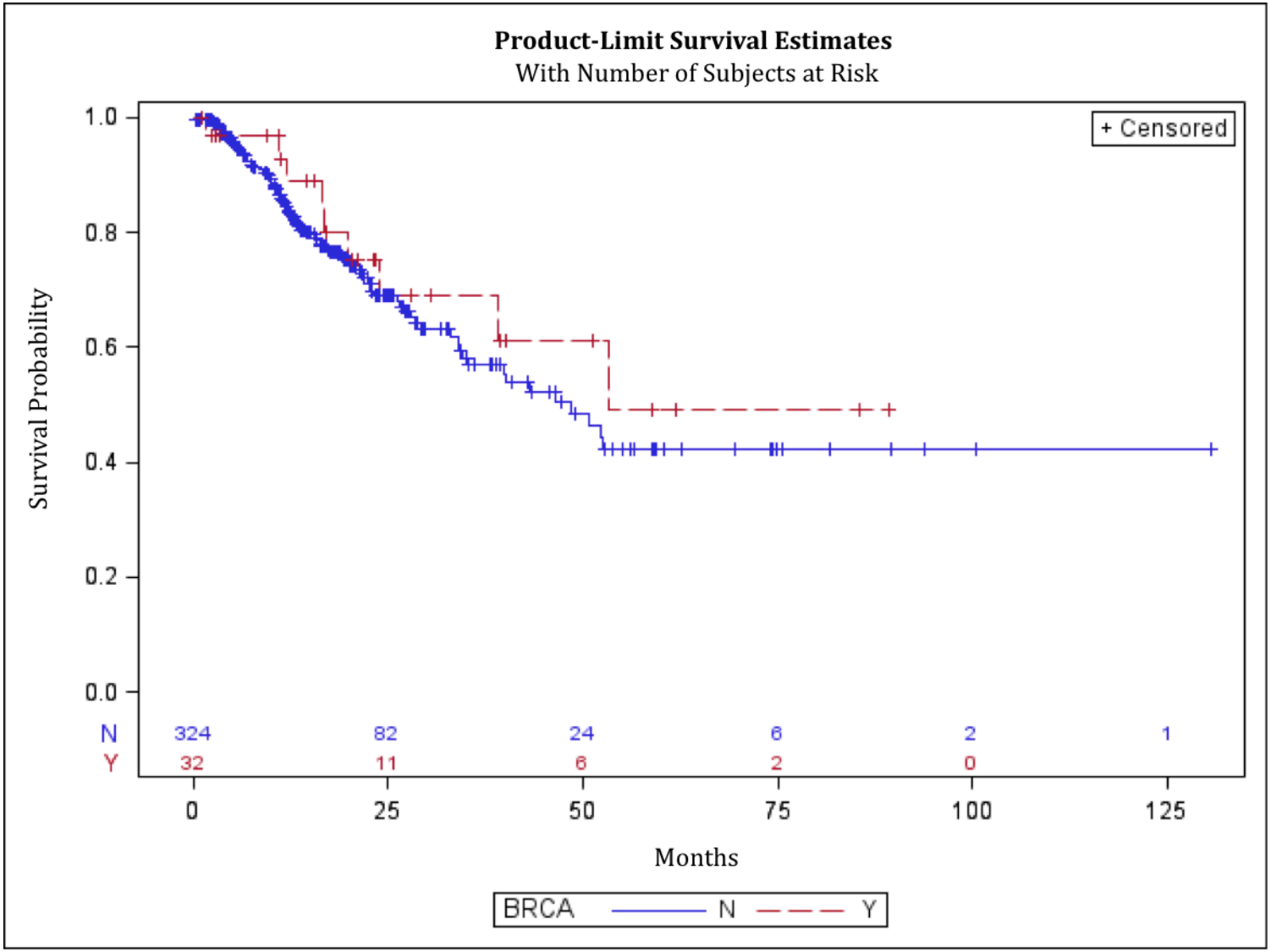
Supplementary Table 5: *BRCA* Mutations Detailed and Response to Platinum*

Gene	N=	Received Platinum	Response	Overall Survival (Months, Median)
BRCA2	18	15 (83.3%)	12 (80.0%)	18
c.5946delT (p.Ser1982Argfs*22)	9	9 (100.0%)	6 (67%)	20
c.4829_4830delTG (p.Val1610Glyfs*4)	1	—	NA	40
c.5569delG (p.Glu1857Lysfs*6)	1	1 (100.0%)	1 (100.0%)	23
c.4638delT (p.Phe1546Leufs*22)	1	1 (100.0%)	1 (100.0%)	10
c.793+1G>A	1	1 (100.0%)	—	11
c.9371A>T (p.Asn3124Ile)	1	—	—	2
c.5614A>T (p.Lys1872*)	1	1 (100.0%)	1 (100.0%)	15
c.6259delA (p.Arg2087Glufs*32)	1	1 (100.0%)	1 (100.0%)	16
c.3847_3848del (p.Val1283Lysfs*2)	1	1 (100.0%)	1 (100.0%)	61
c.3264dupT (p.Gln1089Serfs*10)	1	1 (100.0%)	1 (100.0%)	3
Gene	**N=**	**Received Platinum**	**Response**	**Overall Survival (Months, Median)**
BRCA2 +	4	1 (100.0%)	1 (100.0%)	35
BRCA2 + CHEK2 (c.5946delT + c.1283C>T)	1	—	—	58
BRCA2 + CHEK2 (c.9148C>T + c.1283C>T)	1	—	—	15
BRCA2 + APC (c.5946delT + c.3920T>A)	1	1 (100.0%)	1 (100.0%)	30
*BRCA2 + PMS2 (*c.6468_6469del + c.1831delinsTT)	1			39
Gene	**N=**	**Received Platinum**	**Response**	**Overall Survival (Months, Median)**
BRCA1	10	7 (70.0%)	6 (85.7%)	20
c.427G>T (p.Glu143*)	1	1 (100.0%)	1 (100.0%)	23
c.4986+5G>A	1	1 (100.0%)	1 (100.0%)	51
c.5266dupC (p.Gln1756Profs*74)	2	2 (100.0%)	1 (50.0%)	16
c.65T>C (p.Leu22Ser)	1	—	—	11
c.4524G>A (p.Trp1508*)	1	—	—	85
c.68_69delAG (p.Glu23Valfs*17)	3	2 (67%)	2 (100%)	3
c.181T>G (p.Cys61Gly)	1	1 (100%)	1 (100%)	53

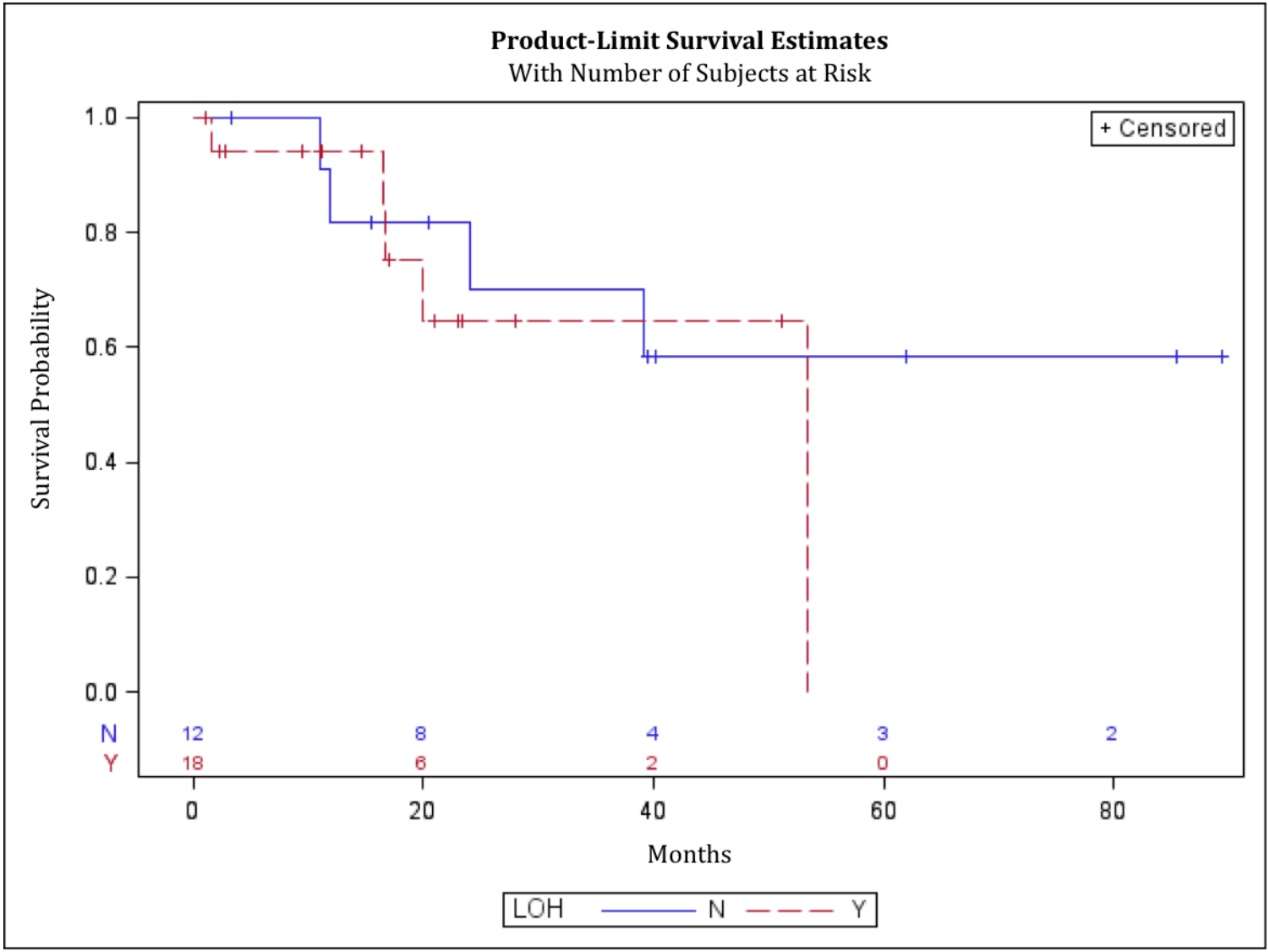
*—denotes 0



Supplementary Figure 1: Spectrum of Pathogenic Germlines Alterations Identified in Entire N= 615 Patient Cohort



Supplementary Figure 2: Kaplan Meyer Curve for N=356 Patients who consented to Germline Testing with and without *BRCA1/2* Mutations from Diagnosis. 324 patients without *BRCA* and 32 patients with *BRCA*.



Supplementary Figure 3: Kaplan Meyer Curve for N=30 Patients with *BRCA1/2* Mutations with and without Loss of Heterozygosity from Diagnosis Date. 18 patients with Loss of Heterozygosity and 12 patients without.