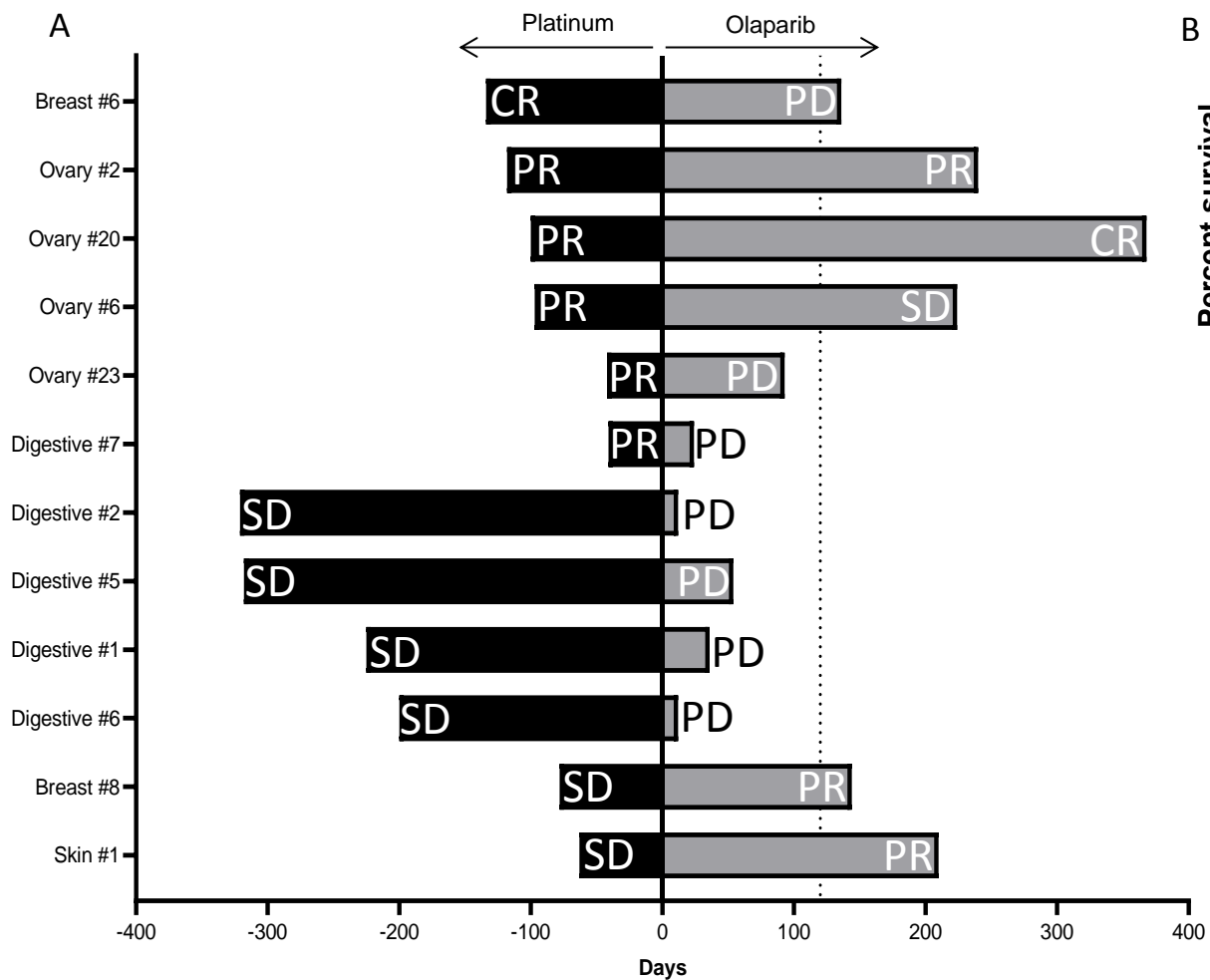
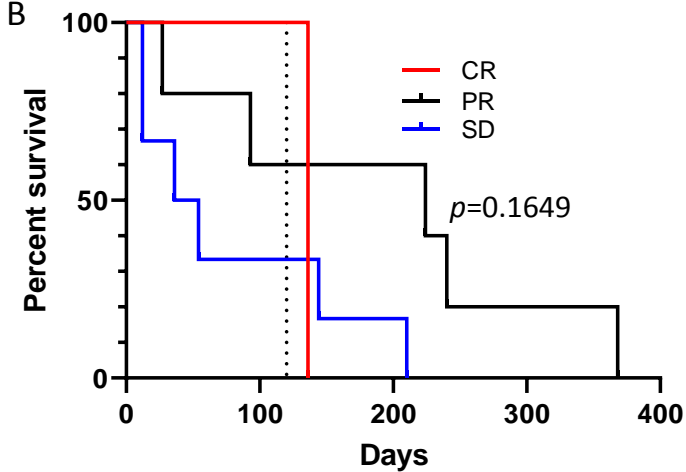


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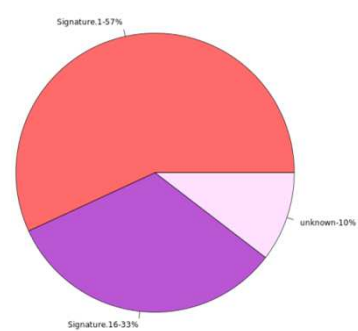
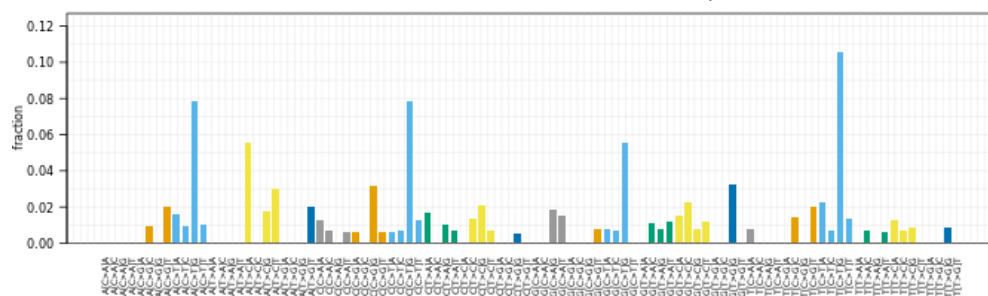


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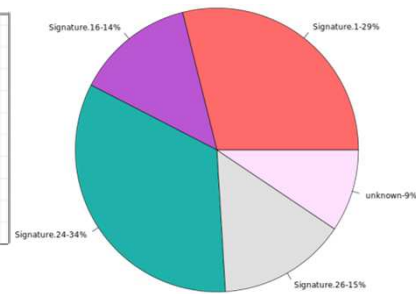
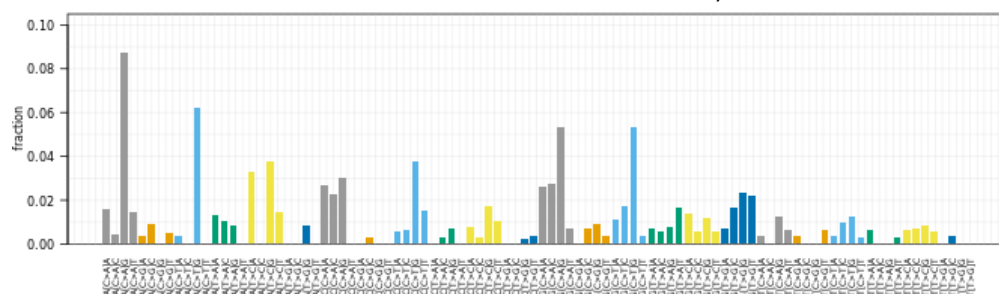


Supplementary Figure S1: Response of VUS to platinum. A. Duration and response (PD: Progressive Disease, SD: Stable Disease, PR: Partial Response, CR: Complete Response) to platinum treatment and subsequent olaparib treatment for VUS. The dashed line corresponds to 120 days. **B.** PFS curve of patients under olaparib treatment depending on their response to platinum based treatment.

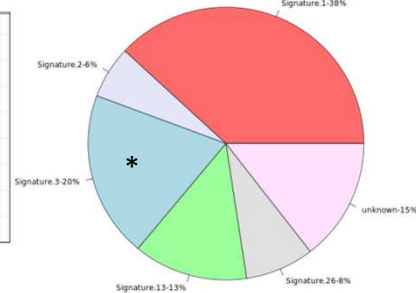
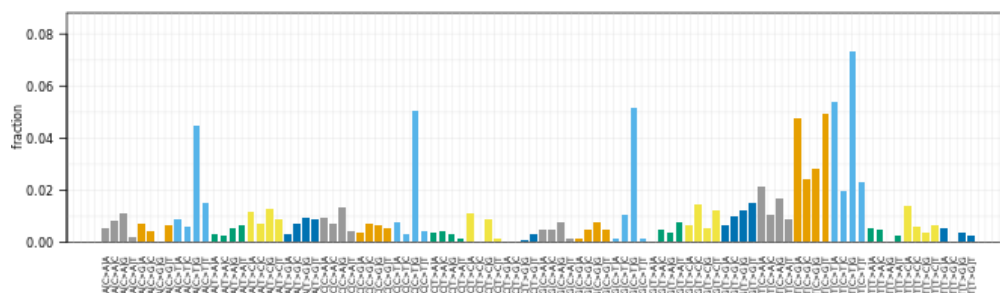
Ovary #19



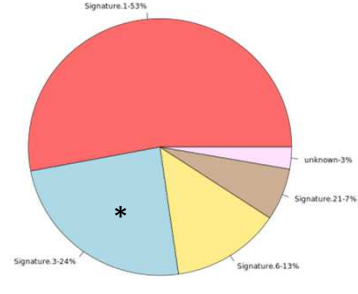
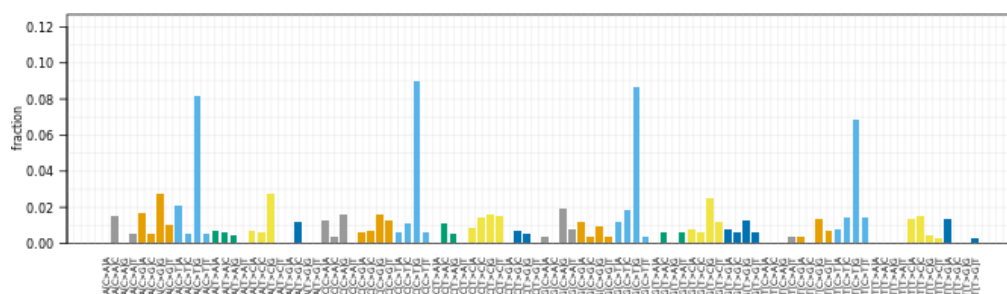
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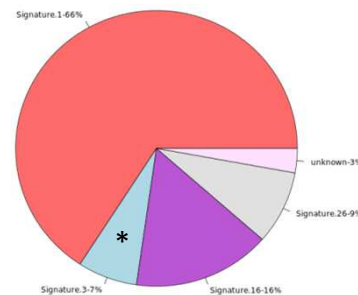
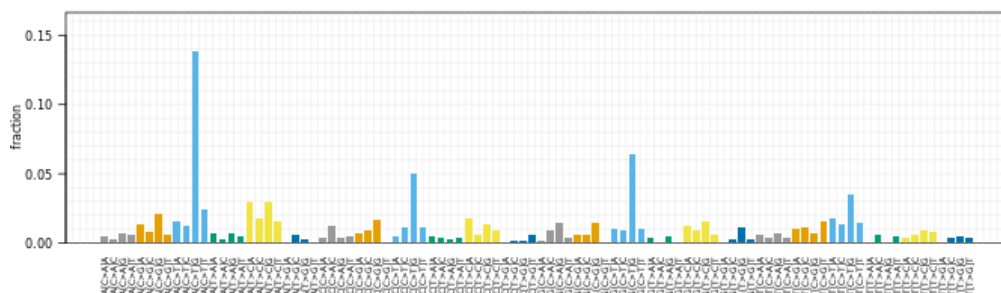
Breast #3



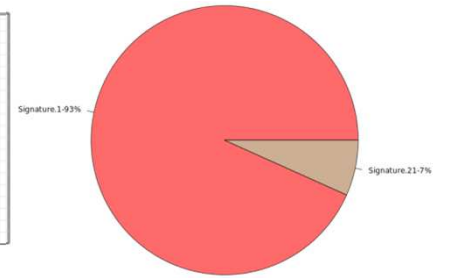
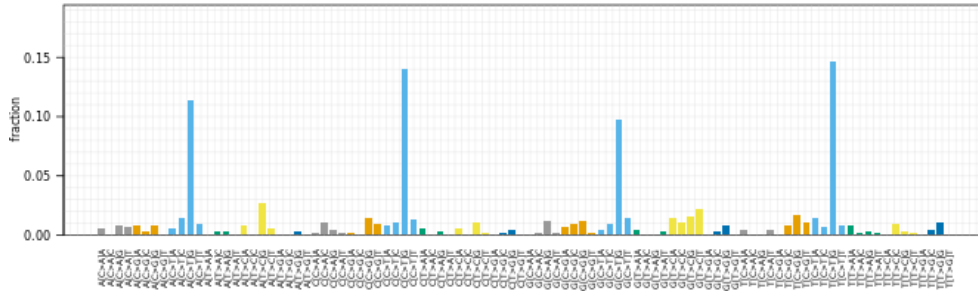
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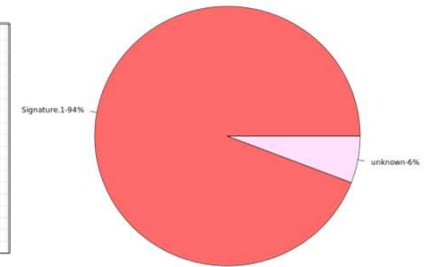
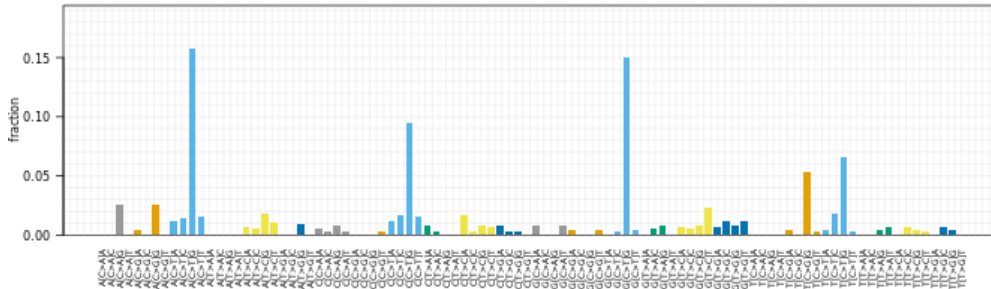
Breast #6



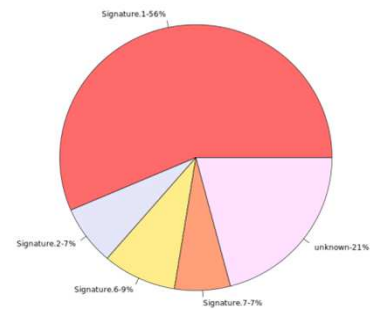
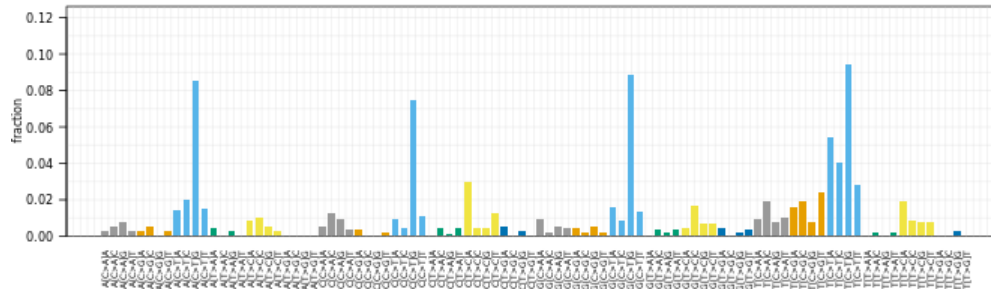
Breast #8



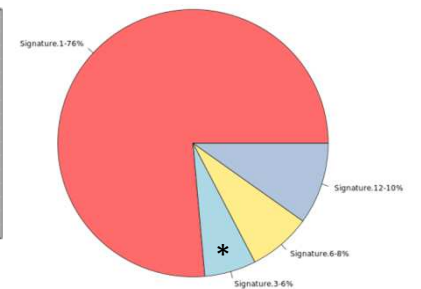
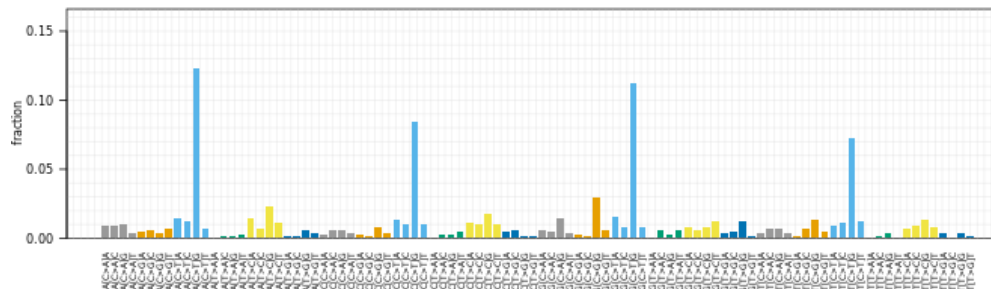
Digestive tract #1



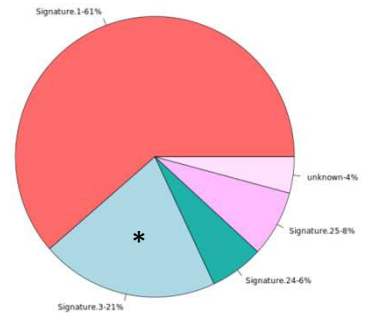
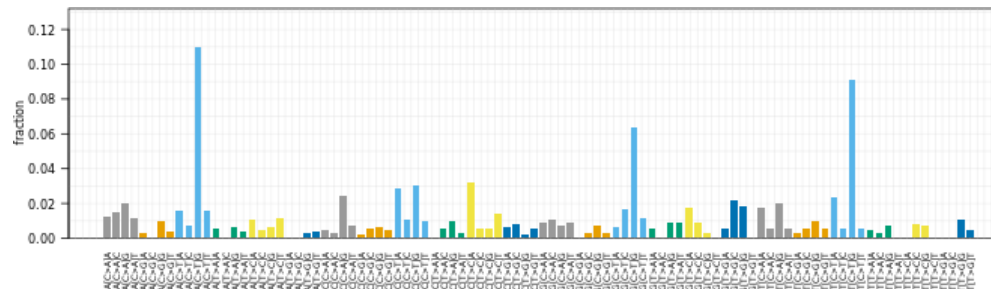
Digestive tract #3



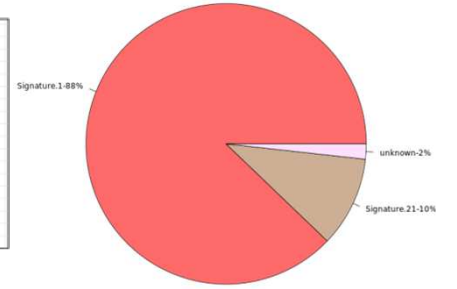
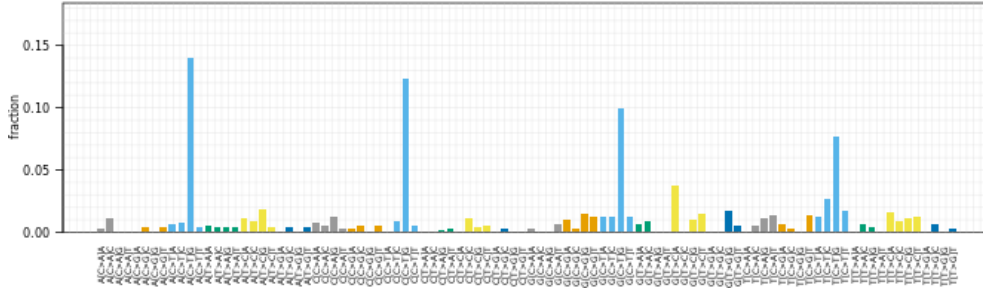
Digestive tract #4



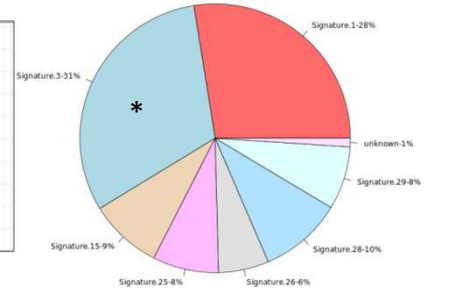
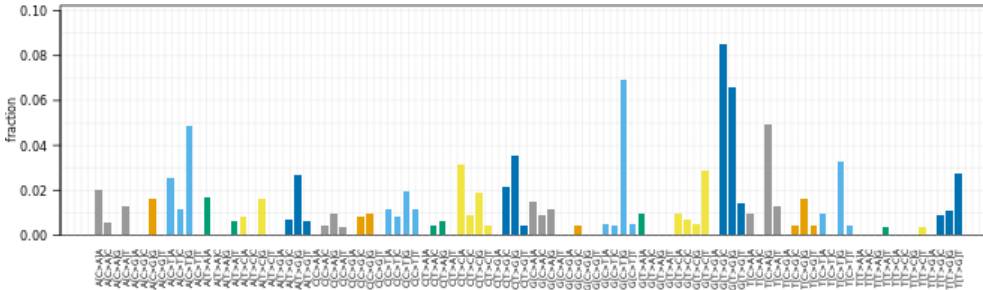
Digestive tract #5



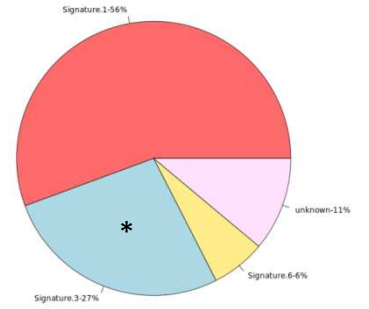
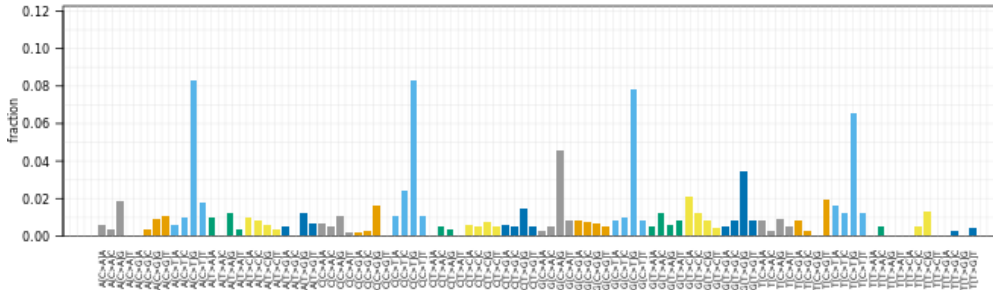
Digestive tract #6



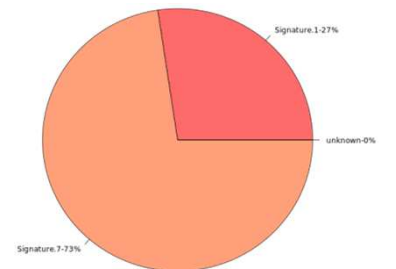
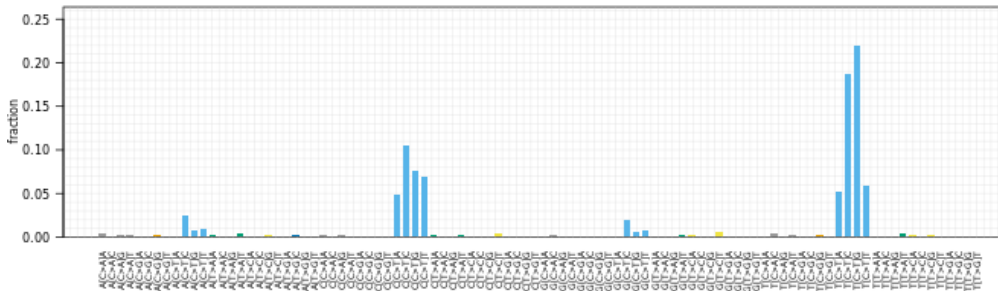
Digestive tract #7



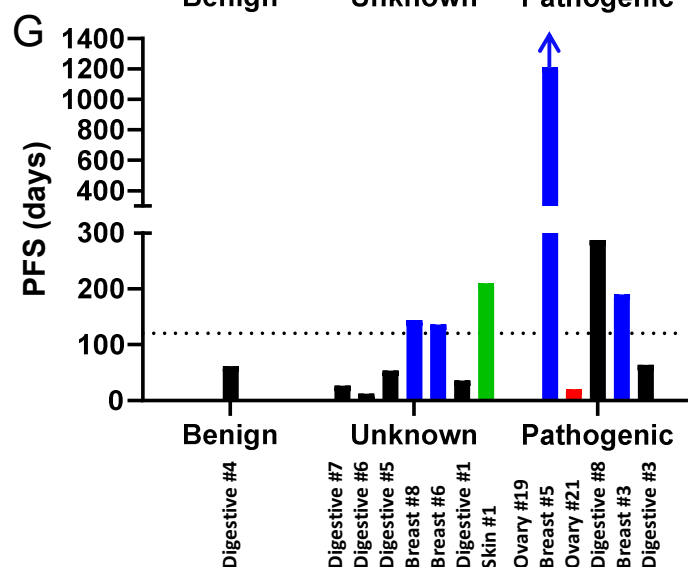
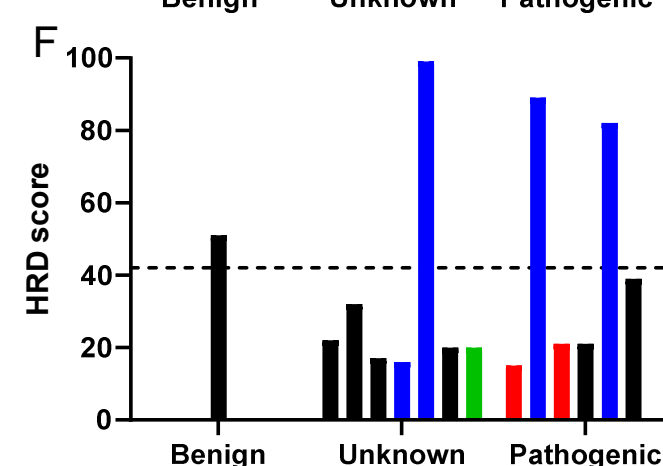
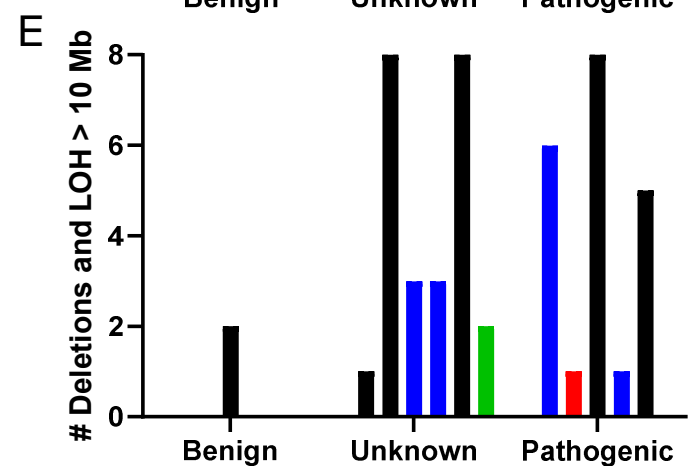
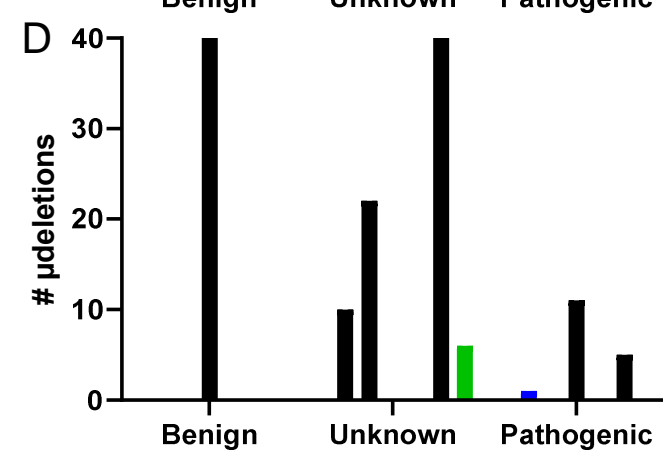
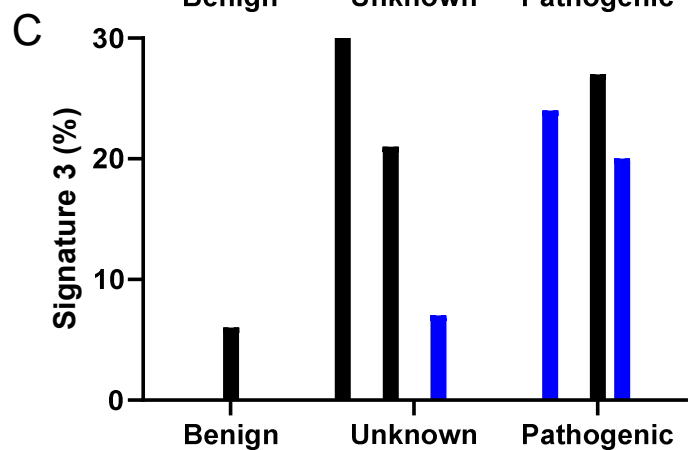
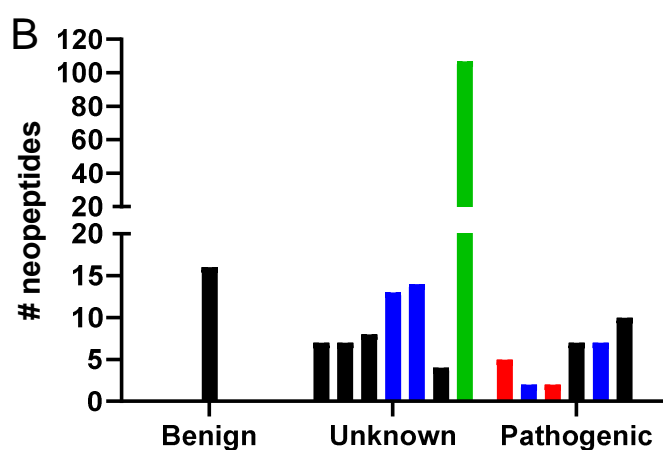
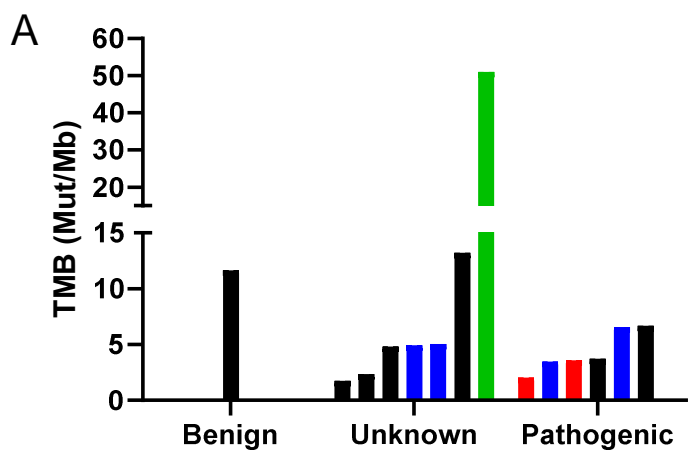
Digestive tract #8



Skin #1

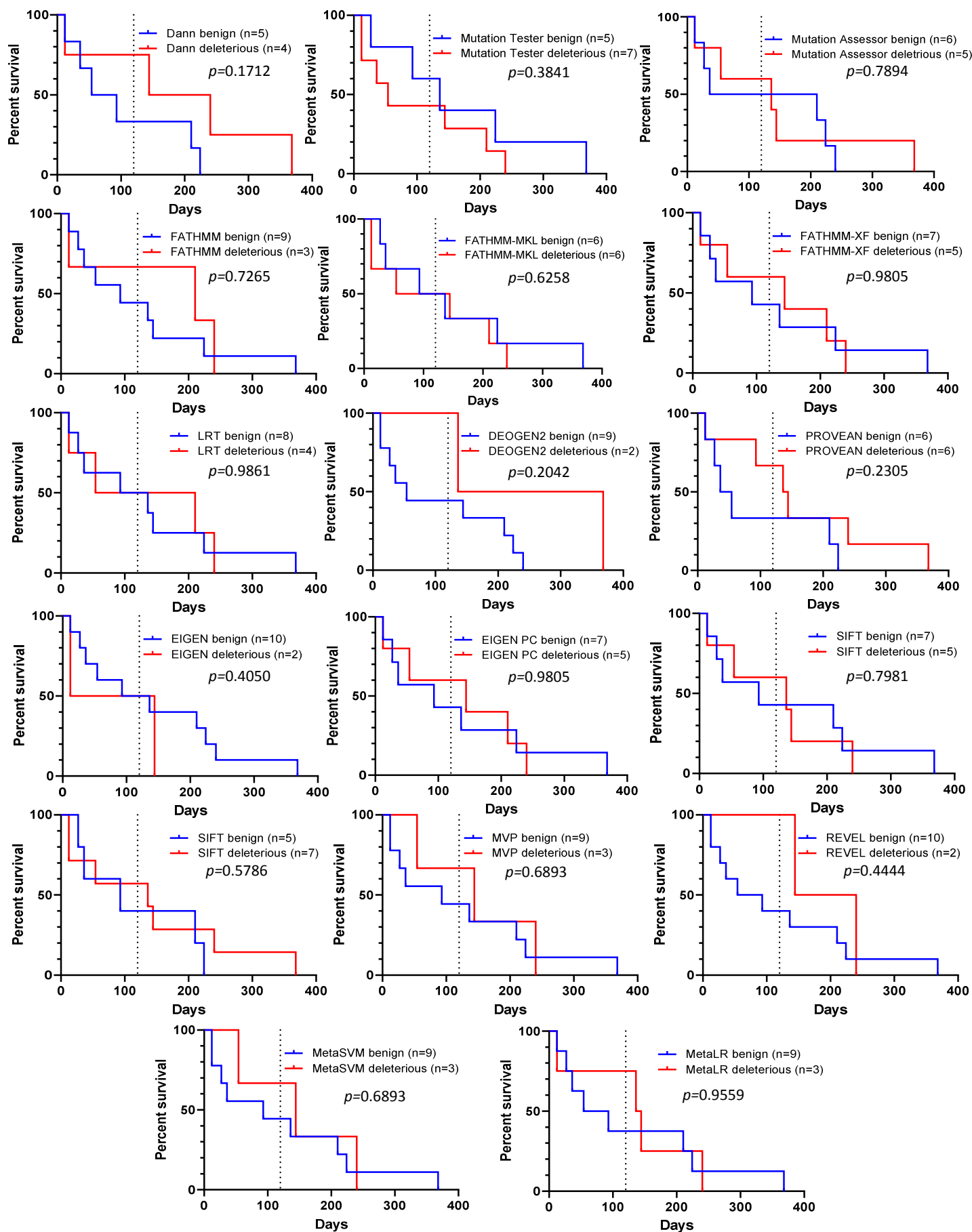


Supplementary Figure S2: Genomic signature profile depending on Alexandrov's work obtained for the 14 patients with both somatic and germline exome analyses. The pie charts indicate the distribution of different signatures bioinformatically detected. Signature 3 is presented in blue and marked with an asterisk.



Digestive #4
Digestive #7
Digestive #6
Digestive #5
Digestive #8
Breast #6
Breast #1
Skin #1
Ovary #19
Breast #5
Ovary #21
Ovary #8
Digestive #3
Breast #3
Digestive #3

Supplementary Figure S3: Graphical presentation of complex analyses obtained from somatic and germline exomes. **A.** Tumor Mutation Burden, **B.** number of neoepitopes, **C.** Alexandrov's signature 3, **D.** number of small deletions, **E.** number of deletions and loss of heterozygosity (LOH) >10 Mb, **F.** HRD score (dashed line corresponds to the official threshold of 42), and **G.** PFS (dashed line corresponds to 120 days, the arrow indicates that olaparib treatment is still ongoing). Patients are classified depending on the official classification of their variants, and in a group from lower to higher TMB. Patients with a digestive tract cancer are in black, patients with a breast cancer are in blue, patients with an ovary cancer are in red and a patient with a skin cancer is in green.



Supplementary Figure S4: PFS under olaparib treatment according to pathogenicity prediction of VUS by 17 *in silico* prediction tools. *In silico* prediction tools are indicated in the legend of each graph. The dashed line corresponds to 120 days.

Supplementary Table S1: Detail of data obtained with the 6 complex analyses from tumor and germline exome sequencing

Cancer type, Patient No.	Gene(s)	Impact	TMB (Mut/Mb)	# Neopeptides	Signature 3 (%)	# μdeletions	# Deletions and LOH > 10 Mb	HRD score	PFS (days)
Ovarian #19	<i>BRCA2</i>	Pathogenic	2.03	5	0	0	0	15	1 (allergic reaction)
Ovarian #21	<i>BRCA2</i>	Pathogenic	3.58	2	0	0	1	21	288
Breast #3	<i>BRCA1</i>	Pathogenic	6.59	7	20	0	1	82	190
Breast #5	<i>BRCA1</i>	Pathogenic	3.48	2	24	1	6	89	1212 (still under olaparib)
Breast #6	<i>BRCA1</i>	Unknown	5.04	14	7	0	3	99	136
Breast #8	<i>BRCA2, RAD51D</i>	Unknown	4.92	13	0	0	3	16	144
Digestive tract #1	<i>PALB2</i>	Unknown	13.23	4	0	41	8	20	36
Digestive tract #3	<i>CHEK2</i>	Pathogenic	6.7	10	0	5	5	39	64
Digestive tract #4	<i>BRCA1</i>	Probably Benign	11.64	16	6	41	2	51	62
Digestive tract #5	<i>BRCA1</i>	Unknown	4.82	8	21	22	8	17	54
Digestive tract #6	<i>BRCA1</i>	Unknown	2.36	7	0	10	1	32	12
Digestive tract #7	<i>BRIP1</i>	Unknown	1.73	7	31	0	0	22	27
Digestive tract #8	<i>ATM</i>	Pathogenic	3.75	7	27	11	8	21	20
Skin #1	<i>PALB2, RAD50, RAD51C</i>	Unknown	51.04	107	0	6	2	20	210

Supplementary Table S2: Prediction of pathogenicity of VUS using different *in silico* tools

Genes	Nucleotide variation	Protein variation	Dann	Mutation Tester	Mutation Assessor	FATHMM	FATHMM MKL	FATHMM XF	LRT	DEOGEN2	PROVEAN prediction
<i>BRCA1</i>	c.53T>C	p.Met18Thr	Pathogenic	Disease causing	Neutral	Damaging	Damaging	Damaging	Deleterious	Tolerated	Damaging
<i>PALB2</i>	c.656A>G	p.Asp219Gly	Neutral	Polymorphism	Neutral	Tolerated	Neutral	Neutral	Neutral	Tolerated	Neutral
<i>BRCA1</i>	c.2744C>T	p.Ser915Phe	Pathogenic	Polymorphism	Medium	Tolerated	Neutral	Neutral	Neutral	Damaging	Damaging
<i>BRCA2</i>	c.1690T>C	p.Met990Lys	Neutral	Polymorphism	Unknown	Tolerated	Neutral	Neutral	Neutral	Unknown	Damaging
<i>BRCA1</i>	c.2783G>T	p.Gly928Val	Unknown	Polymorphism	Medium	Tolerated	Neutral	Neutral	Neutral	Damaging	Damaging
<i>BRCA2</i>	c.4860A>T	p.Leu1620Phe	Neutral	Polymorphism	Unknown	Tolerated	Neutral	Neutral	Neutral	Unknown	Damaging
<i>RAD51D</i>	c.328G>A	p.Asp110Asn	Pathogenic	Disease causing	Medium	Tolerated	Damaging	Damaging	Neutral	Tolerated	Damaging
<i>PALB2</i>	c.2719G>A	p.Glu907Lys	Neutral	Disease causing	Low	Tolerated	Neutral	Neutral	Neutral	Tolerated	Neutral
<i>BRCA1</i>	c.2521C>T	p.Arg841Trp	Neutral	Polymorphism	Low	Tolerated	Neutral	Neutral	Neutral	Tolerated	Damaging
<i>UIMC1</i>	c.1690T>C	p.Tyr564His	Pathogenic	Disease causing	Medium	Tolerated	Damaging	Damaging	Deleterious	Tolerated	Damaging
<i>BRCA1</i>	c.5128A>C	p.Met1710Leu	Neutral	Disease causing	Medium	Tolerated	Damaging	Damaging	Deleterious	Tolerated	Neutral
<i>BRCA1</i>	c.5295A>C	p.Glu1786Asp	Unknown	Disease causing	Low	Damaging	Damaging	Neutral	Neutral	Tolerated	Neutral
<i>BRIP1</i>	c.3G>A	p.Met1?	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*
<i>PALB2</i>	c.2431C>T	p.Pro811Ser	Neutral	Polymorphism	Low	Tolerated	Damaging	Neutral	Neutral	Tolerated	Neutral
<i>RAD50</i>	c.3041A>G	p.Gln1014Arg	Neutral	Disease causing	Low	Damaging	Damaging	Damaging	Deleterious	Tolerated	Neutral
<i>RAD51C</i>	c.584C>T	p.Ala195Val	Neutral	Disease causing	Low	Tolerated	Damaging	Neutral	Deleterious	Tolerated	Neutral

*New in frame initiation codon, 3 codons later.

Genes	Nucleotide variation	Protein variation	EIGEN	EIGEN PC	SIFT	SIFT4G	MVP	REVEL	Primate AI	MetaSVM	MetaLR
<i>BRCA1</i>	c.53T>C	p.Met18Thr	Benign	Pathogenic	Damaging	Damaging	Pathogenic	Pathogenic	Tolerated	Damaging	Damaging
<i>PALB2</i>	c.656A>G	p.Asp219Gly	Benign	Benign	Tolerated	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>BRCA1</i>	c.2744C>T	p.Ser915Phe	Benign	Benign	Tolerated	Damaging	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>BRCA2</i>	c.1690T>C	p.Met990Lys	Benign	Benign	Tolerated	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>BRCA1</i>	c.2783G>T	p.Gly928Val	Benign	Benign	Damaging	Damaging	Benign	Benign	Tolerated	Tolerated	Damaging
<i>BRCA2</i>	c.4860A>T	p.Leu1620Phe	Benign	Benign	Damaging	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>RAD51D</i>	c.328G>A	p.Asp110Asn	Pathogenic	Pathogenic	Damaging	Damaging	Pathogenic	Pathogenic	Tolerated	Damaging	Damaging
<i>PALB2</i>	c.2719G>A	p.Glu907Lys	Benign	Benign	Tolerated	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>BRCA1</i>	c.2521C>T	p.Arg841Trp	Benign	Benign	Damaging	Damaging	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>UIMC1</i>	c.1690T>C	p.Tyr564His	Pathogenic	Pathogenic	Damaging	Damaging	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>BRCA1</i>	c.5128A>C	p.Met1710Leu	Benign	Pathogenic	Damaging	Damaging	Pathogenic	Benign	Tolerated	Damaging	Tolerated
<i>BRCA1</i>	c.5295A>C	p.Glu1786Asp	Benign	Benign	Tolerated	Damaging	Benign	Benign	Tolerated	Tolerated	Damaging
<i>BRIP1</i>	c.3G>A	p.Met1?	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*	Neutral*
<i>PALB2</i>	c.2431C>T	p.Pro811Ser	Benign	Benign	Tolerated	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>RAD50</i>	c.3041A>G	p.Gln1014Arg	Benign	Benign	Unknown	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated
<i>RAD51C</i>	c.584C>T	p.Ala195Val	Benign	Pathogenic	Tolerated	Tolerated	Benign	Benign	Tolerated	Tolerated	Tolerated

*New in frame initiation codon, 3 codons later.