Supplementary Table 1a Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Ovary

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=265	n=15	n=233	n=172	n=61
Gene					
ATM	8	1	7	5	2
BAP1	0	0	0	0	0
BARD1	2	0	1	1	0
BRCA1	114	0	111	81	30
BRCA2	61	0	58	44	14
BRIP1	6	0	5	4	1
CHEK2	3	0	3	2	1
DICER1	3	2	1	0	1
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	6	0	6	4	2
MSH2	4	0	4	1	3
MSH6	9	0	7	4	3
MUTYH	2	0	2	2	0
NF1	9	8	0	0	0
PALB2	7	0	6	6	0
PMS2	1	0	1	1	0
POLD1	1	0	0	0	0
POLE	3	1	2	1	1
PTCH1	3	2	0	0	0
PTEN	1	0	1	0	1
RAD51C	11	0	9	8	1
RAD51D	4	0	4	4	0
RET	2	1	1	1	0
SDHA	2	0	2	2	0
SDHB	2	0	2	1	1
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	1	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1b Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Endometrium

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=147	n=8	n=99	n=48	n=51
Gene					
ATM	27	1	12	4	8
BAP1	0	0	0	0	0
BARD1	3	1	1	0	1
BRCA1	6	0	5	3	2
BRCA2	16	0	9	4	5
BRIP1	3	0	3	1	2
CHEK2	9	0	5	1	4
DICER1	6	2	3	0	3
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	9	0	9	3	6
MSH2	25	0	23	13	10
MSH6	19	0	14	11	3
MUTYH	4	0	4	4	0
NF1	1	1	0	0	0
PALB2	2	0	1	1	0
PMS2	1	0	1	1	0
POLD1	1	0	0	0	0
POLE	2	0	2	0	2
PTCH1	9	3	4	0	4
PTEN	1	0	1	0	1
RAD51C	0	0	0	0	0
RAD51D	1	0	1	1	0
RET	0	0	0	0	0
SDHA	1	0	1	1	0
SDHB	0	0	0	0	0
SDHC	1	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1c Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Lung

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=45	n=5	n=14	n=6	n=8
Gene					
ATM	11	0	4	3	1
BAP1	1	0	0	0	0
BARD1	1	0	0	0	0
BRCA1	5	0	3	2	1
BRCA2	6	0	3	1	2
BRIP1	0	0	0	0	0
CHEK2	2	1	1	0	1
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	1	0	1	0	1
MSH2	0	0	0	0	0
MSH6	2	0	1	0	1
MUTYH	0	0	0	0	0
NF1	6	3	0	0	0
PALB2	3	0	0	0	0
PMS2	0	0	0	0	0
POLD1	1	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	2	0	0	0	0
RAD51D	1	0	1	0	1
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	1	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	1	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	1	1	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1d Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Colorectum

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=26	n=4	n=10	n=5	n=5
Gene					
ATM	4	0	1	0	1
BAP1	0	0	0	0	0
BARD1	2	1	0	0	0
BRCA1	0	0	0	0	0
BRCA2	4	1	2	1	1
BRIP1	3	0	0	0	0
CHEK2	3	1	1	0	1
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	1	0	1	0	1
MLH1	5	0	5	4	1
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	0	0	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	1	1	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	3	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1e Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Pancreas

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=14	n=0	n=10	n=9	n=1
Gene					
ATM	5	0	3	3	0
BAP1	0	0	0	0	0
BARD1	1	0	1	1	0
BRCA1	1	0	1	1	0
BRCA2	4	0	2	2	0
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	0	0	0	0	0
FH	1	0	1	1	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	1	0	1	0	1
MUTYH	0	0	0	0	0
NF1	0	0	0	0	0
PALB2	1	0	1	1	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1f Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Cholangiocarcinoma

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=7	n=0	n=3	n=1	n=2
Gene					
ATM	1	0	0	0	0
BAP1	3	0	2	0	2
BARD1	0	0	0	0	0
BRCA1	1	0	1	1	0
BRCA2	1	0	0	0	0
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	1	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	0	0	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1g Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Melanoma

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=7	n=0	n=2	n=1	n=1
Gene					
ATM	2	0	0	0	0
BAP1	0	0	0	0	0
BARD1	0	0	0	0	0
BRCA1	1	0	1	1	0
BRCA2	1	0	1	0	1
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	2	0	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	1	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1h Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Prostate

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=8	n=0	n=4	n=3	n=1
Gene					
ATM	3	0	1	1	0
BAP1	0	0	0	0	0
BARD1	0	0	0	0	0
BRCA1	0	0	0	0	0
BRCA2	3	0	1	0	1
BRIP1	0	0	0	0	0
CHEK2	1	0	1	1	0
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	0	0	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	1	0	1	1	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1h Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Melanoma

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=7	n=0	n=2	n=1	n=1
Gene					
ATM	2	0	0	0	0
BAP1	0	0	0	0	0
BARD1	0	0	0	0	0
BRCA1	1	0	1	1	0
BRCA2	1	0	1	0	1
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	2	0	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	1	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1i Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Thyroid

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=4	n=0	n=3	n=2	n=1
Gene					
ATM	0	0	0	0	0
BAP1	0	0	0	0	0
BARD1	0	0	0	0	0
BRCA1	0	0	0	0	0
BRCA2	0	0	0	0	0
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	1	0	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	3	0	3	2	1
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1j Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - GIST

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=2	n=0	n=2	n=2	n=0
Gene					
ATM	0	0	0	0	0
BAP1	0	0	0	0	0
BARD1	0	0	0	0	0
BRCA1	0	0	0	0	0
BRCA2	0	0	0	0	0
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	1	0	1	1	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	0	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	1	0	1	1	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 1k Suspected constitutional pathogenic variants according to tumor type and gene involved with an indication to genetic testing - Breast

	Variants with indication to genetic counseling	Variants with no clinical indication to perform germline test	Variants tested in leukocyte DNA		
			All variants	Confirmed	Not confirmed
	n=2	n=1	n=0	n=0	n=0
Gene					
ATM	0	0	0	0	0
BAP1	0	0	0	0	0
BARD1	0	0	0	0	0
BRCA1	0	0	0	0	0
BRCA2	0	0	0	0	0
BRIP1	0	0	0	0	0
CHEK2	0	0	0	0	0
DICER1	0	0	0	0	0
FH	0	0	0	0	0
FLCN	0	0	0	0	0
MLH1	0	0	0	0	0
MSH2	0	0	0	0	0
MSH6	0	0	0	0	0
MUTYH	0	0	0	0	0
NF1	1	1	0	0	0
PALB2	0	0	0	0	0
PMS2	0	0	0	0	0
POLD1	0	0	0	0	0
POLE	0	0	0	0	0
PTCH1	0	0	0	0	0
PTEN	0	0	0	0	0
RAD51C	1	0	0	0	0
RAD51D	0	0	0	0	0
RET	0	0	0	0	0
SDHA	0	0	0	0	0
SDHB	0	0	0	0	0
SDHC	0	0	0	0	0
SMAD3	0	0	0	0	0
SMARCB1	0	0	0	0	0
TSC2	0	0	0	0	0

Results are presented as n (%) except where indicated.

Supplementary Table 2 – Constitutional pathogenic variants detected by additional constitutional testing and/or not fulfilling ESMO criteria

Disease	ID patient	Additional variant #1	Additional variant #2
Primary malignant neoplasm of ovary	1	BRCA1: deletion of exons 18-19	
Primary malignant neoplasm of ovary	2	CHEK2: c.433C>T - p.Arg145Trp	
Endometrial carcinoma	3	MSH2: Exon 16 deletion	
Primary malignant neoplasm of pancreas	4	BRCA1: deletion of exons 1-2	
Endometrial carcinoma	5	MSH2: c.2231T>C - (p.Leu744Ser)	
Primary malignant adenocarcinoma of colon	6	MSH2: c.942+2T>A - p.?	
Primary malignant neoplasm of ovary	7	RAD51C: c.904+5G>T	
Endometrial carcinoma	8	MLH1: c.588+5G>T - p.?	
Endometrioid carcinoma of ovary	9	MSH6: c.3261dup - p.Phe1088fs	
Primary malignant neoplasm of ovary	10	BRCA1: deletion of exons 4-7	
Primary malignant neoplasm of ovary	11	RAD51C: c.904+5G>T	
Primary malignant neoplasm of ovary	12	RAD51C: c.904+5G>T	
Endometrioid carcinoma of ovary	13	MSH6: c.3261dup - p.Phe1088fs	
Endometrial carcinoma	14	MSH2: c.2647dup - p.Ile883fs	
Primary malignant neoplasm of ovary	15	BRCA1: deletion of exons 21-22	CDKN2A: c.301G>T - p.Gly101Trp
Primary malignant neoplasm of ovary	16	BRCA1: deletion of exons 1-2	
Primary malignant neoplasm of ovary	17	BRCA1: deletion of exons 17-18	