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ARTICLE

Molecular Diagnostics

BRCA1/2 in non-mucinous epithelial ovarian cancer: tumour with or without germline testing?

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National guidelines recommend testing all cases of non-mucinous epithelial ovarian cancer (NMEOC) for germline (blood) and somatic (tumour) *BRCA1/2* pathogenic variants (PVs). We performed paired germline and somatic *BRCA1/2* testing in consecutive cases of NMEOC ($n = 388$) to validate guidelines. Thirty-four somatic *BRCA1/2* (s*BRCA*) PVs (9.7%) were detected in 350 cases with germline *BRCA1/2* (g*BRCA*) wild-type. All s*BRCA* PVs were detected in non-familial cases. By analysing our regional germline *BRCA1/2* database there were 92/1114 (8.3%) g*BRCA* PVs detected in non-familial cases (only 3% ≥70 years old) and 245/641 (38.2%) in familial cases. Germline non-familial cases were dominated by *BRCA2* in older women (8/271 ≥ 70 years old, all *BRCA2*). The ratio of s*BRCA*-to-g*BRCA* was ≤1.0 in women aged <70 years old, compared to 5.2 in women aged ≥70 years old ($P = 0.005$). The likelihood of missed germline *BRCA1/2* PVs (copy-number variants missed on most somatic assays) by testing only tumour DNA was 0.4% in women aged ≥70 years old. We recommend reflex tumour *BRCA1/2* testing in all NMEOC cases, and that g*BRCA* testing is not required for women aged ≥70 years old with no identifiable tumour *BRCA1/2* PV and/or family history of breast, ovarian, prostate and/or pancreatic cancer.

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BACKGROUND

Ovarian cancer is the most lethal gynaecological cancer [1]. Despite significant advancements in our understanding of the genetic hallmarks of ovarian cancer histological subtypes, only poly(ADP-ribose) polymerase-1/2 inhibitors (PARPi) are used as standard therapy for genetically stratified tumours, in *BRCA1/2*-mutant (germline [g*BRCA*] or somatic [s*BRCA*]) high-grade serous carcinoma [2–5].

Germline *BRCA1/2* testing is now performed as standard practice following a diagnosis of high-grade serous carcinoma, where g*BRCA* pathogenic variants (PVs) account for ~15–20% of cases [6, 7]. Although the use of PARPi has expanded through oncology-led g*BRCA* testing services, additional tumour *BRCA1/2* testing maximises the utility of PARPi by identifying actionable s*BRCA* PVs [8]. National guidelines recommend testing all cases of non-mucinous epithelial ovarian cancer (NMEOC) for g*BRCA* and s*BRCA* PVs [9–11]. We assessed our experience of paired germline (blood) and somatic (tumour) *BRCA1/2* testing in consecutive NMEOC cases to validate guidelines.

METHODOLOGY

Women diagnosed with NMEOC underwent germline (September 1996 to August 2021) and more recently tumour *BRCA1/2* testing (July 2017 to August 2021) using clinically validated assays in the Manchester Centre for Genomic Medicine. Between July 2017 and August 2021, paired germline and tumour *BRCA1/2* testing could be requested by the treating physician.

The next-generation sequencing (NGS) tumour *BRCA1/2* assay has been previously reported [12, 13]. Briefly, tumour DNA was extracted from formalin-fixed, paraffin-embedded blocks that contained ≥20% tumour content. Bioinformatic analysis used an in-house pipeline validated to detect tumour *BRCA1/2* variants down to an allele frequency of ~4%. The NGS assay detects single nucleotide variants and small duplications, deletions and/or insertions ≤40 base pairs across the whole coding sequence of *BRCA1/2* + /− 15 base pairs beyond exon–intron junctions. Variant allele frequency ≥4% has a call sensitivity >95% and specificity >99% after manual review. Germline *BRCA1/2* testing was performed on DNA extracted from peripheral circulating lymphocytes. The NGS and multiplex ligation-dependent probe amplification (MLPA) assays used to detect g*BRCA* PVs have also been previously reported [14, 15]. The variant interpretation was performed as per published guidelines [16].

Women were considered as 'non-familial' (low familial risk) if they had no more than a single breast cancer themselves or in

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their family diagnosed ≥50 years old. Familial cases included those with more extensive personal and/or family histories of breast, ovarian, prostate and/or pancreatic cancer.

The data included in this study were collected as part of a continuous clinical audit. Clinical data were gathered at the time that the germline and/or tumour *BRCA1/2* status was reported. All patients provided informed consent for blood (germline) and tumour (somatic) *BRCA1/2* testing. Statistical tests used Fisher exact test (two-sided).

RESULTS

Population

One-thousand-seven-hundred-fifty-five women underwent germline testing and 337 were diagnosed with a g*BRCA* PV (g*BRCA1* = 200, g*BRCA2* = 137; prevalence 19.2%); not exclusively in high-grade serous carcinoma (Table 1). Three-hundred eighty-eight women (out of 409; 94.9%) had successful germline and tumour *BRCA1/2* testing ($n = 21$ insufficient material and/or sample failed) (Fig. 1). Initially, samples were tested sequentially with germline *BRCA1/2* testing first ($n = 209$; no tumour testing reported if a g*BRCA* PV was detected) and then testing was carried out either simultaneously or tumour first ($n = 200$).

Thirty-four s*BRCA* PVs were identified in tumour DNA from 350 patients with germline *BRCA1/2* wild-type (s*BRCA1* = 18, s*BRCA2* = 16; prevalence 9.7%; Table 1). All 34 s*BRCA* PVs were detected in non-familial cases (Fig. 1).

Thirty-six g*BRCA* PVs were confirmed in tumour DNA, but two copy-number variants (CNVs) found using MLPA were not identified in tumour DNA, including *BRCA1* Exon 13 duplication ($n = 1$) and *BRCA2* Exons 1–2 deletion ($n = 1$; Table 1). Fifteen (out of 38; 39.4%) g*BRCA* PVs were found in non-familial cases (Fig. 1).

Somatic versus germline *BRCA1/2* pathogenic variants

We used the full germline ($n = 1755$) and tumour ($n = 388$) *BRCA1/2* testing databases to compare the age-specific prevalence of s*BRCA* versus g*BRCA* PVs (Table 1). The most striking difference was found in women aged ≥70 years old, where 17/111 (15.3%) had a s*BRCA* PV (s*BRCA1* = 6, s*BRCA2* = 11) but only 8/271 (3.0%) had a g*BRCA* PV (all g*BRCA2*; Table 1). The s*BRCA*-to-g*BRCA* ratio of 5.2 in women diagnosed with non-familial NMEOC aged ≥70 years old contrasted all other ratios (≤1.0) in women aged <70 years old ($P = 0.005$; Table 1).

Interestingly, there was also a reversal of the g*BRCA2*-to-g*BRCA1* ratio in non-familial NMEOC of 0.8 (25:31) aged <60 years old to 3.0 (27:9) aged ≥60 years old ($P = 0.005$; Table 1).

Miss rate by upfront tumour *BRCA1/2* testing

To assess the potential miss rate of not universally testing all NMEOC cases for germline *BRCA1/2* PVs, we used the full g*BRCA* testing database ($n = 1755$), which included all familial cases. Forty (out of 200; 20%) g*BRCA1* PVs were CNVs, compared to only 5/137 (3.6%) g*BRCA2* PVs. The data suggested only 0.4% of non-familial g*BRCA*-positive CNVs would be missed by testing only tumour DNA in women diagnosed with NMEOC aged >70 years old, but would result in a 1.3% miss rate in those aged <60 years old and 5.0% miss rate in familial cases (Table 1).

DISCUSSION

Tumour *BRCA1/2* analysis of NMEOC cases generally results in g*BRCA* and s*BRCA* PV rates of 15–20% and 5–7%, respectively [6, 15, 17–19]. However, germline rates in non-familial NMEOC, even in high-grade serous carcinoma, are much lower, particularly in those diagnosed >60 years old [14, 20]. Indeed, age ≥70 years old in one study found only 1/86 of unselected cases of NMEOC had a g*BRCA* PV [20]. Our rate of 3% (8/271) in women diagnosed ≥70 years old was made up entirely of g*BRCA2* PVs, which contrasted with the age of onset with g*BRCA1* PVs [21].

Thus far, the age of onset of s*BRCA* has not been correlated, but we found an almost double rate of somatic *BRCA1/2* PVs diagnosed ≥70 years old. This means that only one in six *BRCA1/2* PVs found on tumour analysis in non-familial NMEOC cases ≥70 years old will be germline. Whilst national guidelines recommend initial g*BRCA* testing, a more practical approach would be to start with reflex tumour *BRCA1/2* testing (by pathologists) of all cases of NMEOC, particularly in those women diagnosed ≥70 years old. This would enable a timely result to facilitate PARPi maintenance therapy, thereby avoiding the delays/misses/refused cases with germline *BRCA1/2* testing. Indeed, the tumour *BRCA1/2* testing assay described in this study has a turnaround time of 21 to 28 days, and testing can be requested immediately following histological diagnosis. Moreover, tumour *BRCA1/2* testing may not require specific consent, and even if consent is required this should not entail a detailed discussion about personal and/or familial risks. In practice, discussions about inherited risk can be particularly worrying for women who are simultaneously trying to deal with the diagnosis and treatment of ovarian cancer.

The high ratio of s*BRCA*-to-g*BRCA* PVs in non-familial cases aged >70 years old is an interesting finding from our study. The likelihood of somatic variants in oncogenes and/or tumour suppressor genes increases with age, potentially due to faltering DNA repair mechanisms. Therefore, more s*BRCA* PVs are likely to be detected in older age groups. Moreover, the increase in s*BRCA1/2* PVs is offset by a lower prevalence of g*BRCA1/2* PVs. Indeed, the risk of hereditary ovarian cancer does not increase with age >50 years old, and cases of g*BRCA*-mutant NMEOC aged >70 years are reduced by the competing mortality from breast cancer and/or risk-reducing bilateral salpingo-oophorectomy in younger heterozygotes.

Given the extremely low chance of missing a g*BRCA* PV on tumour *BRCA1/2* testing in women diagnosed ≥70 years old (0.4%; in UK costs approximately £500,000 per CNV) it is arguable whether a germline (blood) sample is required unless a tumour *BRCA1/2* PV is detected and/or tumour testing fails. However, in younger women and especially those with a family history, miss rates could be as high as 5.0% if CNVs are not reliably detected through tumour *BRCA1/2* testing [8, 19, 22–24]. It is therefore essential that germline *BRCA1/2* testing is carried out on all familial cases and those diagnosed <60 years old. Rates of germline *BRCA1/2* CNVs vary from 3–5% in *BRCA2* to 10–20% in *BRCA1*, reflecting the sensitivity of detection.

It is notable that our study only reports the incidence of *BRCA1/2* PVs in NMEOC cases. Indeed, consideration should be given for extended panel testing to detect germline PVs in moderate-to-low penetrance genes associated with hereditary ovarian cancer (e.g., *RAD51C/D*, *BRIP1*, *PALB2*) in *BRCA1/2* wild-type cases with a family history of cancer. Although we are not recommending extended panel testing for all NMEOC cases with *BRCA1/2* wild-type, we do recommend referral to Clinical Genetics for those women who have a first-degree or second-degree relative with ovarian cancer.

It is also noteworthy that there may be a degree of selection bias in our study. Firstly, for those women in whom a g*BRCA* PV was detected prior to completion of tumour testing (i.e., sequential or simultaneous germline/tumour testing versus tumour first), if a germline PV was reported first, it would halt additional unnecessary reporting of tumour variants. Therefore, it is likely that more than 409 cases of NMEOC had paired germline/tumour testing requested. This factor explains the relatively low prevalence of g*BRCA* PV detected in the paired testing cohort (9.3%; 38/409) versus the full germline database (19.2%; 337/1755). Secondly, if tumour tissue was not available; for example, due to cytological diagnosis and/or low tumour cell content following diagnostic workup, then only germline *BRCA1/2* testing could take place, meaning the somatic status of some g*BRCA* wild-

Table 1. Germline and somatic *BRCA1/2* pathogenic variants by age and familial situation with germline miss rates and somatic-to-germline ratios.

	Non-familial OC (low familial risk)						Familial OC	Combined total	HGSC	CCC	EOC	Carcinosarcoma	Other
	Age (years)					Total							
	<30	30–49	50–59	60–69	70 +								
Full germline *BRCA1/2* testing database ($N = 1755$)													
Germline *BRCA1/2* tested (no.)	18	199	319	325	271	1114	641	1755	1512	61	108	23	51[d]
g*BRCA1/2* wild-type (no.)	18	177	285	297	263	1022	396	1418	1197	55	97	18	51[d]
g*BRCA1* PV (no.)	0	12	19	9	0	40	160	200	188	4	7	1	0
%[a]	0.0%	6.0%	6.0%	2.8%	0.0%	3.6%	25.0%	11.4%	12.4%	6.6%	6.5%	4.3%	0.0%
g*BRCA2* PV (no.)	0	10	15	19	8	52	85	137	127	2	4	4	0
%[a]	0.0%	5.6%	5.3%	6.4%	3.0%	5.1%	21.5%	9.7%	10.6%	3.6%	4.1%	22.2%	0.0%
Combined g*BRCA1/2* PV (no.)	0	22	34	28	8	92	245	337	315	6	11	5	0
% Combined g*BRCA1/2* PV[a]	0.0%	11.1%	10.7%	8.6%	3.0%	8.3%	38.2%	19.2%	20.8%	9.8%	10.2%	21.7%	0.0%
Successful paired tumour and germline *BRCA1/2* testing cohort ($N = 388$)													
BRCA1/2 tested (no.)	0	42	82	107	112	343	45	388	361	9	15	1	2
g*BRCA1/2* PV confirmed (no.)	0	5	3	6	1	15	23	38	32	1	3	0	0
g*BRCA1/2* wild-type (no.)	0	37	79	101	111	328	22	350	327	8	12	1	2
g*BRCA1/2* PV missed in tumour DNA (no.)	0	0	0	2[b]	0	2[b]	0	2[b]	2[b]	0	0	0	0
% g*BRCA1/2* PV Missed	0.0%	0.0%	0.0%	33.3%	0.0%	13.3%	0.0%	5.3%	5.9%	0.0%	0.0%	0.0%	0.0%
s*BRCA1* PV (no.)	0	3	3	6	6	18	0	18	18	0	0	0	0
%[c]	0.0%	8.1%	3.8%	5.9%	5.4%	5.5%	0.0%	5.1%	5.5%	0.0%	0.0%	0.0%	0.0%
s*BRCA2* PV (no.)	0	1	1	3	11	16	0	16	15	1	0	0	0
%[c]	0.0%	2.7%	1.3%	3.0%	9.9%	4.9%	0.0%	4.6%	4.6%	12.5%	0.0%	0.0%	0.0%
Combined s*BRCA1/2* PV (no.)	0	4	4	9	17	34	0	34	33	1	0	0	0
% Combined s*BRCA1/2* PV[c]	0.0%	10.8%	5.1%	8.9%	15.3%	10.4%	0.0%	9.7%	10.1%	12.5%	0.0%	0.0%	0.0%
s*BRCA*-to-g*BRCA* ratio	0.0	1.0	0.5	1.0	5.2	1.3	0.0	0.5	0.5	1.3	0.0	0.0	0.0
Missed rate g*BRCA1/2* CNVs	0.0%	1.3%	1.2%	0.7%	0.4%	0.9%	5.0%	2.4%	2.7%	1.8%	1.3%	0.9%	0.0%

CCC clear cell carcinoma, *CNVs* copy-number variants, *EOC* endometrioid ovarian carcinoma, *g*BRCA germline *BRCA1/2*, *HGSC* high-grade serous carcinoma, *no.* number, *OC* ovarian cancer, *PV* pathogenic variant, *s*BRCA somatic *BRCA1/2*.

[a]The denominator is the number of cases tested for germline *BRCA1/2* pathogenic variants.

[b]Two cases of non-mucinous epithelial ovarian cancers had a copy-number variant detected in germline DNA but not in tumour DNA.

[c]The denominator is the number of cases tested for tumour *BRCA1/2* pathogenic variants with confirmed germline *BRCA1/2* wild-type.

[d]Includes $n = 11$ and $n = 2$ low-grade serous carcinoma cases who underwent blood (germline) and tumour (somatic) testing, respectively, as well as adenocarcinoma otherwise specified (NOS).

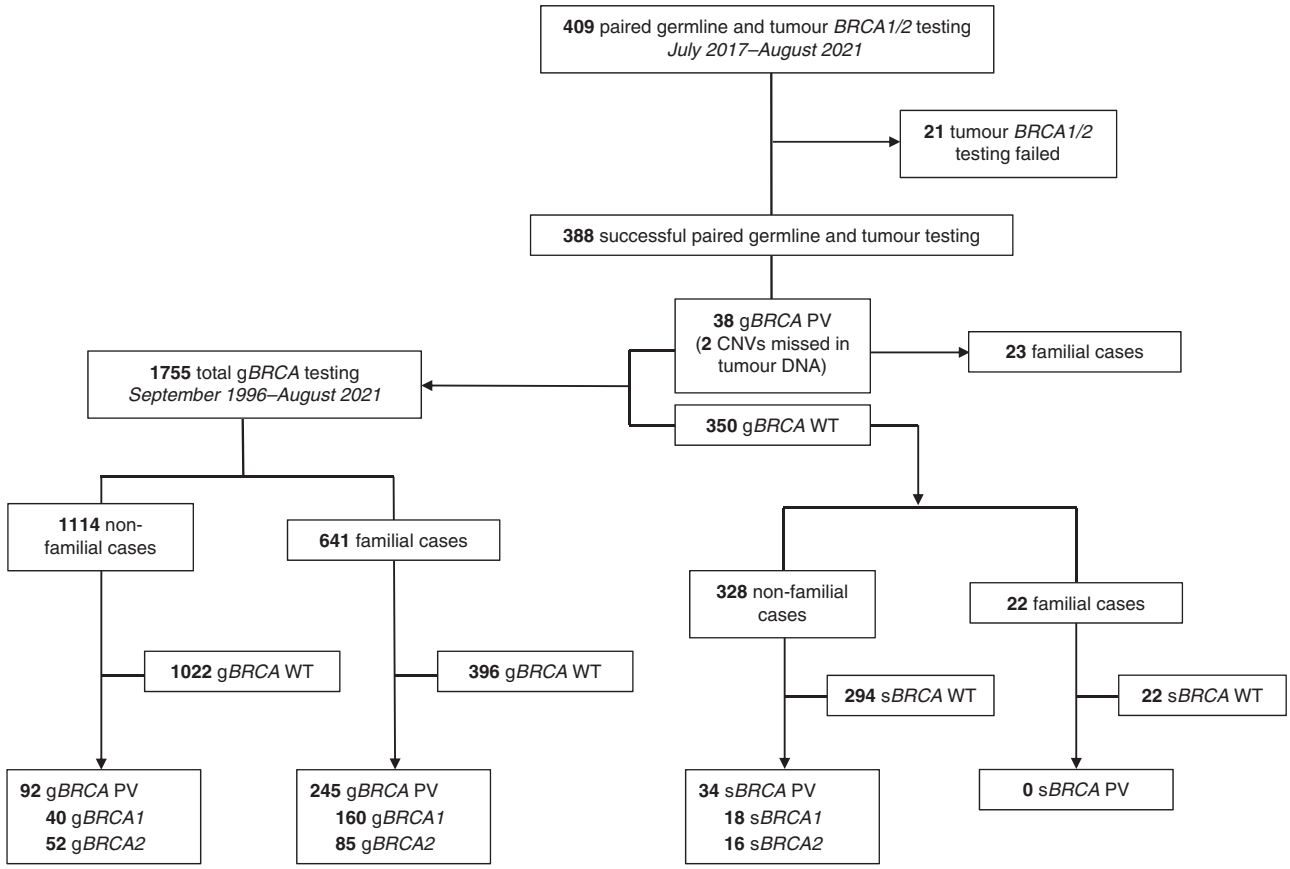

Fig. 1 Flow chart for germline and tumour *BRCA1/2* testing. Paired germline and tumour testing was requested in 409 patients. In total, 1755 patients underwent germline testing.

type cases remains unknown. This factor may explain the relatively high prevalence of s*BRCA* PVs detected in the paired testing cohort (9.7%; 34/350).

In conclusion, we report the detection rate of s*BRCA* PVs with paired blood (germline) and tumour (somatic) DNA testing in a large cohort of NMEOC cases. We recommend starting with tumour *BRCA* testing, and that germline testing is probably not indicated after confirming tumour *BRCA*1/2 wild-type in women diagnosed with NMEOC aged ≥70 years and no family history of breast, ovarian, prostate and/or pancreatic cancer.

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AUTHOR CONTRIBUTIONS

RDM and DGRE designed and initiated the study. RDM, NF, ARC, JH, CLM, ZS, ERW, FL, EJC, RJE, GCJ and DGRE gained consent for germline and tumour *BRCA1/2* testing. GJB, MB, PS and AJW reported all germline and tumour *BRCA1/2* results. All authors interpreted the data and reviewed the final version of the manuscript.

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COMPETING INTERESTS

RDM, GJB, NF, MB, PS, JH, CLM, ZS, ERW, FL, EJC, RJE, AJW and DGRE declare no competing interests. GCJ declares research funding from AstraZeneca for investigator-led clinical trials. ARC declares research funding and advisory boards fees from AstraZeneca, and speaker and advisory board fees from Clovis Oncology.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All women included in this study provided informed consent to undergo germline and tumour *BRCA1/2* testing. The germline *BRCA1/2* database is approved by North Manchester Research Ethics Committee (08/H1006/77). The Genetic Variants in Gynaecological Cancer database is approved by the Christie NHS Foundation Trust (59).

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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